Volume 27, Number 6, June, 1955

The Yale Journal of Biology & Medicine

395 **URINARY LITHOTRESIS ESPECIALLY WITH ULTRASOUND** *Harold Lamport and Herbert F. Newman*

432 **EFFECTIVENESS OF THORIUM DIOXIDE AS AN ALPHA EMITTER** *Hermann J. Schaefer and Abner Golden*

441 **MENDELIAN RECESSIVE TRAITS AND FIBROSARCOMA RESISTANCE** *Frank L. Gruskay and Leonell C. Strong*

451 **EVALUATION AND MANAGEMENT OF HYPERTENSION** *Allan V. N. Goodyer, Ernest Rosenthal, and Carl A. Jaeger*

487 **EVENTS**

491 **BOOK REVIEWS**

503 **INDEX TO VOLUME 27**

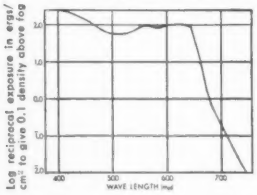
Kodak reports to laboratories on:

red light and recording film . . . getting rid of hypo with less time and water . . . a lightweight among the fats

"Linagraph": its meaning

This is a warning to anyone who constructs a hood out of clear red plastic to permit watching a cathode-ray display while it is being photographed, as suggested by a recent helpful hint in *Science* on electrophysiological recording: watch out. The premise, "since Linagraph paper and film are both insensitive to red light," is defective. Linagraph Paper and *some* Linagraph Film are insensitive to red; but *Kodak Linagraph Pan Film*, the film most likely (on the basis of our sales figures) to be in your recording camera, is sensitive to red even more, proportionally, than the human eye.

Here is its spectral response:



Even now we are getting ready a faster *Linagraph* film than this, and most assuredly that too will have red sensitivity. With c-r beams writing at hundreds of inches per microsecond, sensitivity is what you dearly want in a film. Moreover, there are cases where the longer wavelength portion of the sensitivity serves specifically to record the persistent component of the emission from some phosphors.

Kodak Linagraph Ortho Film, the second best seller, has negligible red sensitivity so that it should require no filter to remain unaffected by the reddish cathode glow.

No hard feelings, of course. What if a product naming committee of a large manufacturing firm does devise a word like "Linagraph" as a trade-mark to cover the firm's whole diverse group of instrument-recording films and papers? Users of the products who find that word on non-red-sensitive film or paper can hardly be blamed for using it to identify these materials when writing for colleagues about their use. On the contrary, they ought to be thanked and hereby are.

For nothing more than the trouble of writing Eastman Kodak Company, Graphic Reproduction Division, Rochester 4, N. Y., anyone can get a pamphlet that gives all the tedious but helpful facts about Kodak Linagraph Films and Papers.

Of time and water

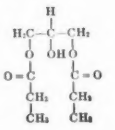
The purpose of washing film or paper after fixation is to remove hypo. The longer and more vigorous the wash, the less hypo is left. Ordinarily 0.10 mg of anhydrous sodium thiosulfate per square inch of film emulsion is considered a tolerable residual. For archival storage, one may wish to reduce the residual to as little as one-fifth of that. You pay for your time and water, and you take your choice. In a well-equipped laboratory the choice is easy, but there are places on earth where men who process photographic materials cannot get all the tempered water they want by merely turning it on.

Now along comes *Kodak Hypo Clearing Agent* to displace hypo by a pre-wash and bring the residual down lower than it would otherwise go with twice as much washing time and water.

It's designed for film but works also for *Kodak Linagraph Papers*. Two minutes in a solution of the new preparation and eight minutes of washing get the hypo out of these papers more completely than a full hour of vigorous washing in just water. And while plain water doesn't wash very well at temperatures near freezing, the new stuff works as well at 35 F as at 70 F.

Kodak Hypo Clearing Agent *is now sold by Kodak dealers in package sizes sufficient to prepare 5 or 25 gallons of solution.*

Artificial fat



To one on the threshold of an investigator's career, what a chance *Dipropionin* offers to flex the muscles and dry the wings!

Think of it! A most unnatural fat, obtainable, so far as we know, from no other source on land or sea! In this newly added Practical Grade Eastman Organic Chemical (Eastman P7041) he will find monopropionins, dipropionins, and tripropionins, in which the dipropionins take the lead, with glycerine and propionic acid far in the rear.

As a partial glyceride, *Dipropionin* might be expected to have interesting interfacial properties. It is notably less miscible with water than is *Diacetin* (Eastman P85). With these physical properties and the odd-length carboxylic chain giving rise to inimical metabolic intermediates, an investigator might look for biological action much different from that of better known fats. In fact, we have a suspicion (only a suspicion, we repeat) that this is a likely place to look for highly reactive free propionyl radicals.

Whether the radicals are free or not, the mobile liquid they may or may not come in costs $6.10 for 100 grams. Our List No. 39 of some 3500 organic chemicals we stock is free. You get the chemical or the catalog from Distillation Products Industries, Eastman Organic Chemicals Department, Rochester 3, N. Y. (Division of Eastman Kodak Company).

Price is subject to change without notice.

This is one of a series of reports on the many products and services with which the Eastman Kodak Company and its divisions are . . . *serving laboratories everywhere*

Kodak
TRADE-MARK

CONTENTS

395 **A CRITICAL APPRAISAL OF METHODS FOR DISRUPTION AND EXTRACTION OF URINARY CALCULI, ESPECIALLY WITH ULTRASOUND** *Harold Lamport and Herbert E. Newman*

432 **THE EFFECTIVENESS OF COLLOIDAL THORIUM DIOXIDE AS AN INTERNAL ALPHA EMITTER: A COMBINED MORPHOLOGIC AND RADIOAUTOGRAPHIC STUDY** *Hermann J. Schaefer and Abner Golden*

441 **CORRELATION BETWEEN MENDELIAN RECESSIVE TRAITS AND THE RESISTANCE TO FIBROSARCOMA IN MICE** *Frank L. Gruskay and Leonell C. Strong*

451 **THE CLINICAL EVALUATION AND MANAGEMENT OF HYPERTENSION**

Part I. Evaluation of the Definition, Etiology, and Prognosis of Hypertension *Allan V. N. Goodyer*

Part II. Evaluation of Fundoscopic Findings in Hypertension *Ernest Rosenthal*

Part III. Medical Treatment of Hypertension *Carl A. Jaeger*

487 **EVENTS**

491 **BOOK REVIEWS**

i **INDEX TO VOLUME 27**

THE YALE JOURNAL
OF BIOLOGY AND MEDICINE

Founded in 1928.

George H. Smith; *Editor-in-Chief, 1928-49; Editor-in-Chief Emeritus, 1949-52.*

BOARD OF EDITORS

Paul B. Beeson; Peter Blos, Jr.; Levon Z. Boyajian; Richard I. Breuer; Padraic Burns; Joseph C. Cerny; Edward D. Coppola; Milton Corn; Ronald H. Fishbein; Marie-Louise Johnson; Frederick G. Kilgour, *Managing Editor;* Peter H. Klopfer; James W. Lewis, *Advertising Manager;* Averill A. Liebow; Vernon W. Lippard, *Chairman;* C. N. H. Long; Myron M. Lotz; Guy M. McKhann; Roy Schafer; Max Taffel; Elizabeth H. Thomson, *Assistant Editor;* Talbot H. Waterman

---

Subscriptions. THE YALE JOURNAL OF BIOLOGY AND MEDICINE is published in September, November, December, February, April, and June from 333 Cedar Street, New Haven 11, Connecticut, U.S.A. The subscription price for one volume of six issues is $6.00 in the United States, $7.50 in other countries. For students registered in any school of Yale University, the subscription price is $4.00 per volume. Single copies are $1.50 each except for special issues.

Entered as second-class matter January 11, 1929, at the post office at New Haven, Connecticut, under the Act of March 3, 1879.

PRINTED BY THE VAN DYCK PRINTING CO., NEW HAVEN, CONN.

Upjohn

Bacterial diarrheas...

Kaopectate

Trademark, Reg. U.S. Pat. Off.

with Neomycin

Each fluidounce contains:

Neomycin sulfate 300 mg. (4⅔ grs.)
[equivalent to 210 mg. (3¼ grs.) neomycin base]
Kaolin . . . . . 5.832 Gm. (90 grs.)
Pectin . . . . . 0.130 Gm. (2 grs.)
Suspended with methylcellulose 1.25%

Supplied:

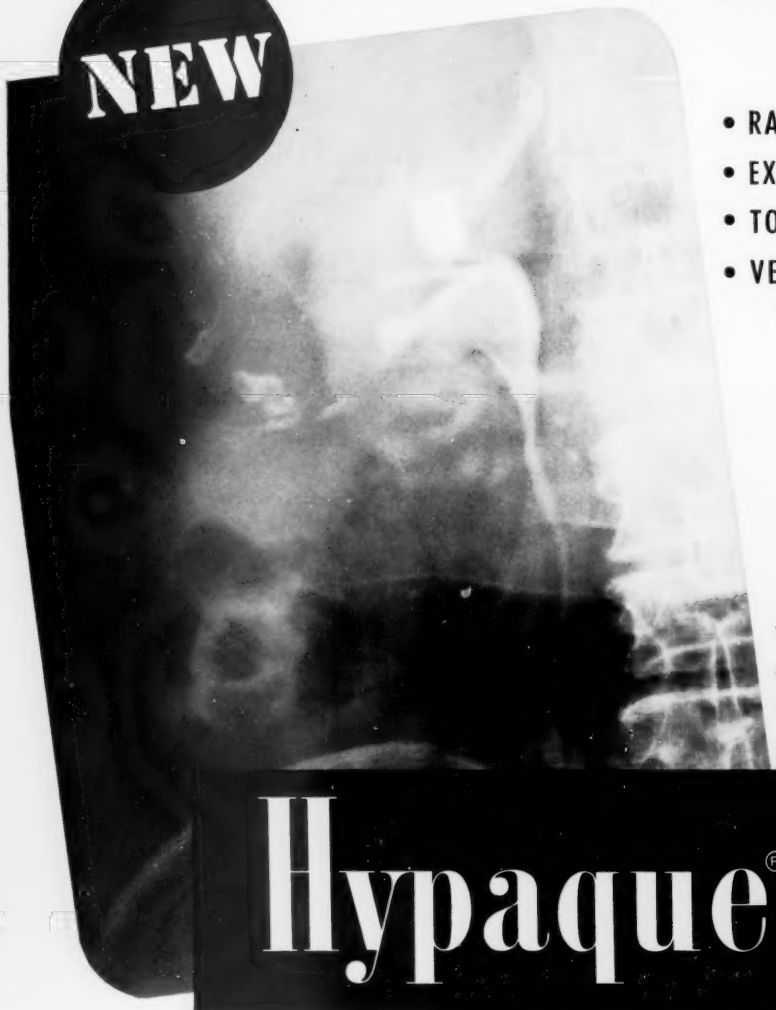
6-fluidounce and pint bottles

The Upjohn Company, Kalamazoo, Michigan

"Substantial Progress"*

IN EXCRETORY UROGRAPHY

NEW



- RADIOPACITY..*High*
- EXCRETION..*Rapid*
- TOXICITY..*Low*
- VEIN CRAMP..*Rare*
  (in approximately 1% of cases)

Write for detailed literature.

Hypaque® SODIUM

SUPPLIED: 50% sterile aqueous solution, ampuls of 30 cc., boxes of 1, 10 and 25 (with 1 cc. test ampuls).

*Moore, T. D.; and Mayer, R. F.: Hypaque: An Improved Medium for Excretory Urography. A Preliminary Report of 210 Cases. Paper read at 48th Annual Meeting of Southern Medical Assn., St. Louis, Mo., Nov. 10, 1954.

Hypaque, trademark reg. U.S. Pat. Off., brand of diatrizoate

"In addition to the excellent quality of excretory urograms obtained with Hypaque the virtual absence of major side effects and the small percentage of minor side effects were notable."*

Winthrop-Stearns INC.
NEW YORK 18, N. Y. WINDSOR, ONT.

HAROLD LAMPORT*
HERBERT F. NEWMAN†

Department of Physiology, Yale University, New Haven, and Gouverneur Hospital, New York City

A CRITICAL APPRAISAL OF METHODS FOR DISRUPTION AND EXTRACTION OF URINARY CALCULI, ESPECIALLY WITH ULTRASOUND‡

This paper reviews the problem of the manipulative treatment of urolithiasis by mechanical means designed to fragment and bore through the stone with the purpose of facilitating its passage out of the urinary tract. To a varying extent, the different facets of the methods outlined are analyzed critically. Some facets have been explored in pilot experiments with a view to estimating their immediate or ultimate promise. In one instance, using ultrasound, the method is deemed to have clinical promise so that our experience with it is reported in some detail. Except within the bladder, lithotresis, as far as we have been able to determine, has not been considered for therapy of urolithiasis. Browne refers to it casually as a harmless incident in ureteral stone removal.[8]

I. INTRODUCTION

Much of the practice of urology is concerned with the treatment of the patient with urinary calculi, whether in bladder, kidney, or ureter.

Stones in the bladder are passed spontaneously, crushed with the lithotrite inserted through the urethra, or removed surgically. The various means of lithotresis (i.e., the drilling or boring of holes in a stone) to be described can be applied with obvious modifications to bladder calculi more easily, we believe, than to those in the ureter. We have confined our attention to ureteral calculi because they are most important clinically. Except for one possibility to be mentioned later, none of the methods considered for ureteral lithotresis seems particularly applicable to renal calculi, unless their location in the renal pelvis makes them similar to those in the ureter. Breaking a renal calculus large enough to impact in the ureter has the danger of producing fragments which may themselves impact in the ureter.

---

* Research Associate in Physiology.
† Attending Surgeon, Gouverneur Hospital, New York City.
‡ Supported by a research grant A-106C from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, Public Health Service, and by a gift from Mrs. Martha Johnson. The views expressed here are solely the authors'.

Received for publication April 29, 1955.

Copyright 1955 by THE YALE JOURNAL OF BIOLOGY AND MEDICINE, INC.

The therapy of ureteral calculi consists of expectant observation, since approximately half the stones are expelled spontaneously as a result of urine flow and ureteral peristalsis.[23, 19] If spontaneous passage fails, the urologist may choose cystoscopic manipulation and if unsuccessful, operative removal. The larger the stone and the nearer the kidney, the greater the likelihood that surgery is deemed necessary.[29, 19, 11] Kittredge and James[19] report, with the concurrence of Priestley,[29a] that "stones lodged in the upper or middle third of the ureter . . . [should be removed surgically since] manipulation is impractical because of their position." They regard stones larger than three-fourths of a centimeter as requiring surgery. Ellik manipulates stones up to one centimeter anywhere in the ureter, preferably with his looped catheter.[13, 29b] Although passing catheters and dilators[12] up to the stone but not beyond sometimes promotes passage of the calculus, forceful extraction, whether by multiple catheters entwined about the stone, by the wire or nylon basket, or by the looped catheter, requires bypassing the stone.[29b, 11, 20]

The distribution of calculi in the ureter depends to some extent on the source of the clinical material. Kittredge and James[19] reported 19 per cent of 274 stones were in the upper third of the ureter, 8 per cent in the middle third, and 73 per cent in the lower third. Ninety-four per cent of stones in the upper third and all in the middle third of the ureter obstructed it. Very few of these calculi were passed spontaneously. In marked contrast, stones in the lower third often descended unaided and were in general less likely to obstruct or to require operation because of the failure of manipulation. We thus see that better methods to aid in manipulative treatment of large or obstructing calculi in the upper and middle segments of the ureter would have a welcome place in the urologist's armamentarium.

Drugs, chemicals, and diets to promote the solution of urinary stones have been tried for hundreds of years.[7, 16, 18, 38] Currently, the organic acid and synthetic amino acid chelating substances are exciting interest.[2, 27, 30, 31, 1] If irrigation with dissolving fluids is to be used, knowledge of the chemical composition of the stone and also unrestricted time are required. At present, success is limited to certain types of urinary calculi, especially calcium phosphate, and irritation of the mucosa may be prominent.[29c] Since temporizing in the face of renal obstruction is universally deplored,[20, 29a] the frequent occurrence of obstructing calculi further reduces the number of cases suitable for calculus solution. Although chelating substances excreted by the kidney, such as hyaluronic acid resulting from injected hyaluronidase, may have prophylactic value,[9, 10] they rarely dissolve stones.[29d]

Mineralogic classification of urinary calculi has now been authoritatively recorded by Prien and Frondel.[25, 34] The nucleus of many urinary calculi is crystalline rather than organic.[28] The majority of calcium oxalate stones, which are physically the hardest to crush, are formed on a calcium phosphate nucleus.[29d]

II. CONSIDERATION OF VARIOUS MECHANICAL MEANS TO PROMOTE MANIPULATIVE TREATMENT OF URETERAL LITHIASIS

Our interest in ureteral lithiasis was stimulated in 1949-50 when we found that gallstones could be fragmented, suspended, and dissolved under the influence of intense ultrasound (400 kc. and higher frequencies).[22] We then proposed the use of much lower frequencies of pulsed ultrasound produced by magnetostriction to be applied by a transducer and probe in direct contact with urinary calculi with the aim of fragmenting them so that their passage or removal might result.[21]

In our consideration and appraisal of the various routes to lithotresis, some have not been pursued for practical reasons, others for scientific or clinical reasons. Nonetheless, although we have achieved a measure of success in lithotresis in cadavers with a particular method, we believe that other routes outlined here may prove fruitful and perhaps superior in the clinic. We hope that several methods of lithotresis, each with its particular merits, will be brought into clinical practice.

CHELATING FLUIDS WITH ULTRASOUND

Since ultrasound also promotes solution, the various slow-acting chelating fluids proposed for dissolving urinary calculi may act faster with its concomitant use. Such a method, of obvious applicability to bladder stones, may be of especial value for renal calculi, where direct contact of an ultrasonic probe with the stone may be difficult, inadequate, or inadvisable.* Although chelating fluids after prolonged application are irritating to mucosa, it is possible that the shorter contact required with low frequency (25 kc.) ultrasound may be less irritating. Even though high frequency ultrasound (1000 kc.) promotes the penetration of drugs into tissues, low frequency ultrasound may not act this way. *In vitro,* we have found that ultrasound speeded up the solution of a "stone" composed of plaster-of-Paris (calcium sulfate) and calcium oxalate in equal parts in a 5 per cent

* This method in cadaver experiments has been found promising in treating biliary calculi via the Best T-tube biliary tract drain.

solution of a mixture of disodium and trisodium *Sequestrene** proportioned to give a pH of 7.2.

Should the removal of all the fragments into which a calculus is broken become a problem, either because they are not all removed by simple irrigation and spontaneous passage, or because a residual fragment may act as a nidus for a new calculus[21, 15, 39] despite subsequent dietary, drug, and fluid prophylaxis, then chelating fluids with ultrasound may well complement lithotresis.

NON-ULTRASONIC LITHOTRESIS

Ultrasound is a dramatic and almost magical modality. To guard against its charms, we have considered other mechanical means so that a simpler method of ureteral lithotresis would not be overlooked. In each instance, we recognized that the lithotresic motion sought might be produced at the calculus by (i) a mechanical contrivance, (ii) by a mechano-electric transducer, or (iii) outside the body, merely being transmitted through urethra, bladder, and ureter to the stone.

A. *Unidirectional rotation.* Dentistry uses rotating chrome steel and tungsten carbide bits to drill the hardest tissue in the human body, the teeth. Flexible cables to transmit torque, rotating in sheaths like speedometer cables, are available. The smallest size cable made was brazed onto an arrow-pointed, wedge-shaped, chrome drill† with an intervening bronze sleeve (see Fig. 1). We found the cable in a light polyethylene no. 7 Fr.‡ sheath was not too large to pass through the ureter of an anesthetized dog, but that it was too stiff, vibrated excessively, and would perforate the ureter if pressed against it. Also, it was difficult to start the drill into the stone, since the drill tended to spin off and bypass it. Urinary calculi, however, drill rapidly.§ This method of conveying mechanical energy to a device within the ureter we regard as valuable; if it could be effectively and harmlessly utilized in the small space available, it would have the advantage of rugged simplicity. The rotating drill seems particularly well-suited to bladder lithotresis.

---

* *Sequestrene* is a trade-name for ethylene bisimino-diacetic acid.

† We are indebted to Mr. Leendart Verkuil, an accomplished jeweler's instrument maker, for assembling this device.

‡ The designation *Fr.* will be implied but omitted hereafter when sizes are noted. No. 7 Fr. means a tube of 7 mm. external circumference.

§ We wish to thank the various hospitals in Connecticut which sent us urinary calculi in response to our appeal. Dr. Hubert Hecht generously donated his collection of urinary stones.

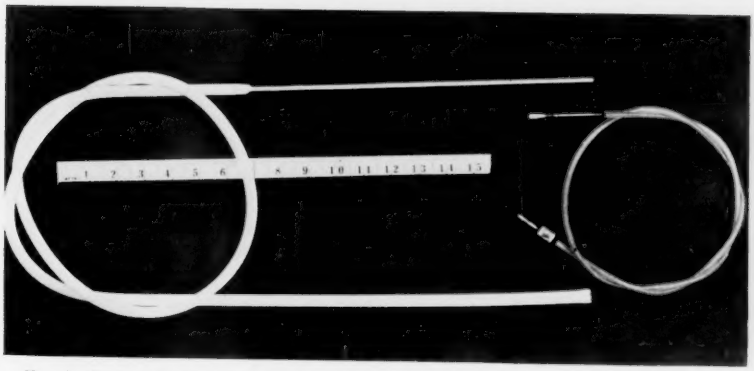


FIG. 1. *Right side.* Rotating drill and flexible cable in plastic sheath. *Left side.* Metal, spiral-wound catheter partially sheathed in plastic. (The devices are coiled only for purposes of illustration.)

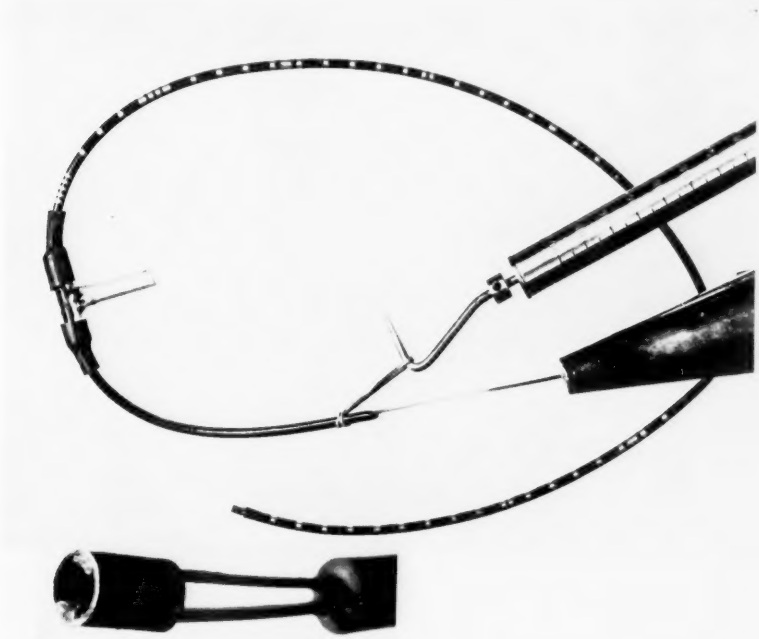


FIG. 2. Components of ureteral ultrasonic lithotresor. A monel cone is soldered to four monel ribbons which pass through a no. 11 catheter to a monel tube drill tip, shown enlarged. There are small holes in the last four inches of the drill end of the catheter not revealed in the figure. A T-tube opposite an eye in the catheter transmits vacuum to its lumen. A spring balance applies drilling force to the catheter by means of the rubber band. (The catheter is shown coiled only for purposes of illustration.)

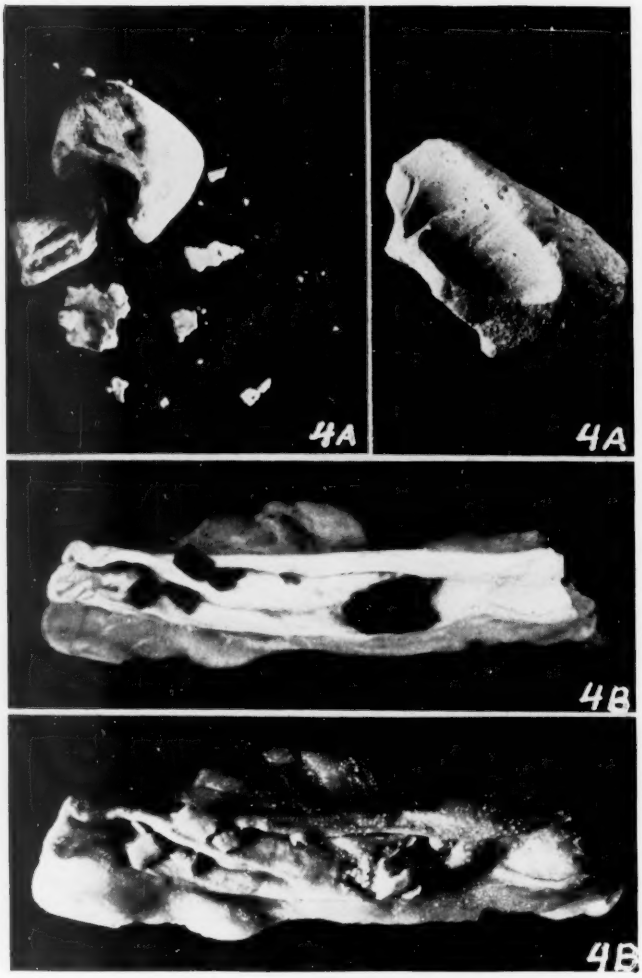


FIG. 4A. Two artificial ureteral stones bored and fragmented by ultrasonic lithotresor in cadaver. The concavity in each specimen corresponds to the drill size, 3.2 mm. in diameter (no. 10 French).

FIG. 4B. Cadaver ureter split open after lithotresis of artificial stone. The upper photograph was taken under ultraviolet light to increase the contrast between ureter and the bored stone with its fragments, since plaster, in contradistinction to ureter, does not fluoresce. The lower photograph was made with normal illumination.

A tiny, high-speed, water turbine dental drill has been developed at the National Bureau of Standards. It stops instantly when pressed against soft tissue, certainly a necessity if it were to be applied blindly in the ureter. But it requires a higher rate of water flow than is acceptable in the ureter. In the bladder, a high flow rate may not be objectionable.

We concluded that unidirectional rotating drills were not at present as promising as other methods of ureteral lithotresis, although they may have importance for bladder lithotresis.

B. *Vibrating rotation.* Plaster casts and, in the autopsy room, skulls are cut by a saw which vibrates back and forth through so short a stroke (perhaps 3 mm.) that soft tissue is not damaged, since it vibrates with the saw instead of being cut. Would not a drill rotating back and forth act similarly, drilling solid urinary stones effectively while leaving the elastic ureter unscathed?

If the rotary oscillation is produced outside the body, a single or multiple wire transmission line to the drill would be needed. Where the oscillation is of such low frequency that the distance to the drill is small compared to the wave length of the rotary oscillation, the problem of transmission would not be too formidable, but drilling speed might be low. At high frequencies, the transmission of a torsional wave along a wire with the development in it of standing torsional waves is an intriguing physical problem, the analogue of the transmission of compressional ultrasonic waves along a wire to be considered later. The torsional standing waves that might be generated for use in lithotresis would, we believe, be of less energy content than compressional ultrasound. Furthermore, since the drill would remain constantly in contact with the stone, we suspect that this method would not drill as efficiently as the ultrasonic drill.

Conceivably, torsional electro-mechanical transducers small enough to fit into the ureter can be designed, since there are ceramics, crystals, and magnetostrictive designs in which this mode of vibration can be induced electrically. The difficulty would be in attaining mechanical resonance at a frequency low enough to provide sufficient amplitude of rotation in the small space available.

We have not experimented with rotary oscillation; the technical pioneering required does not appear justified.

C. *Lateral, scratching vibration.* This type of motion is the one utilized in the cast cutter already mentioned. Again, the difficulties are mechanical and the modality does not offer high efficiencies. A flexion or transverse wave can easily be transmitted along a wire, but its wave-length and energy content, as with the torsional wave, are low compared to the compressional

wave. We have measured the flexural wave-length in bare wires by dripping water along them; droplets are found only at the nodal points, half a transverse wave-length apart. The ultrasonic flexion waves in wire drilled poorly, presumably since they carry so little energy and do not retract the drill periodically in the hole. Furthermore, a bent catheter easily damps them out.

Unless a flexion transducer of proper size and amplitude of vibration can be made to fit inside the ureter, we do not consider this mode of lithotresis promising.

D. *Longitudinal, compressional coaxial vibration.* Such motion is like that of a pneumatic stone drill or riveting hammer. At low sonic frequencies, drilling of stone is quite satisfactory. The problem is to obtain forceful coaxial vibration at a drill in contact with a ureteral calculus.

A device was constructed in which a spring-loaded plunger was pressed against a rotating but slightly canted disc. By varying the speed of the motor and the distance from the plunger to the axis of rotation of the disc, frequency and amplitude were controlled. A single wire attached to the plunger and passed through a catheter drilled effectively, but flexibility of the combination was poor. This was due to the fact that a properly flexible wire loaded by being pressed into the material to be drilled translated its coaxial vibration into marked flexion waves which caused excessive vibration without drilling.

A trial was made of transmitting sonic vibrations through water in a catheter, originating them in a waterproof, dynamic loudspeaker motor. This method was not pursued further because of its many technical problems. Our theoretical analysis suggested that it would be possible, however, to transmit sonic energy in useful amounts to the tip of a nondistending catheter terminating in a drill mounted on a diaphragm, selecting a frequency which would make the speaker-catheter-drill combination a resonant transmission line with one or more standing waves, the diaphragms at each being at anti-nodal points. A problem, as ever, is the design of the drill end. A short, extensible tube (really a kind of diaphragm) continuous with the inextensible catheter and terminating in the drill tip may serve well. Following the principle underlying the operation of the Bourdon gauge, pressure waves in a bent tube will tend to vary its flexion, using up some of the energy by converting it into transverse vibrations of the tube. How serious an objection this might be, we have not estimated. Such a system might also require a degassed and even pressurized fluid to avoid cavitation and consequent transmission losses.

The flexible, unidirectional rotating cable in a catheter might produce the desired coaxial vibration at its tip, but again the difficulties of mechanical design in the small space available are formidable.

E. *Hydraulic jet.* A high-speed water jet, like that delivered by the needleless hypodermic syringe and used in mining, will drill stones and penetrate soft tissue. Only in the guarded location of the bladder, would such a method of lithotresis be safe; we have not tested it.

ULTRASONIC LITHOTRESIS

We found that ultrasound activating a wire in compressional vibration, similar to the pneumatic stone drill used in excavating but at much higher, inaudible frequencies (15 to 45 kc. per second), drilled urinary calculi better wet than dry, and best when flushed with water. Could this vibration be generated in the ureter at the stone? Could it be generated outside the body and transmitted through a catheter to the stone drill?

A. *Ultrasonic transducer in ureter.* In order to gain experience with ultrasonic production and in the hope that the power requirements for drilling were not high, we sought to have a barium titanate transducer mounted on the end of a special catheter whose walls incorporated an electrical conductor. The patient's body was to serve as an electrical ground. Ultrasonic electrical oscillations are too rapid to stimulate tissues. The projected transducer would not resonate at the low ultrasonic frequencies at which drilling occurs so that its efficiency would have been extremely low. The manufacturer failed in successive attempts to make this transducer. With our present experience with such devices, we doubt that it would have been effective and have not returned to it.

The great length of elastic solid required to obtain resonance at low frequencies precludes intra-ureteral, electromechanical, resonant transducers unless a radically new idea is originated.

Ultrasonic whistles powered by water have been invented but they have a low power efficiency and require an inordinately large rate of water flow, considerably greater than is possible for the ureter. We have made a model of a new type of water whistle, which it is hoped can be improved to the point where it may be feasible to use in the ureter.

B. *Ultrasonic transmission in fluids to ureter.* Just as sonic frequencies may be transmittable in a fluid to a drill at the end of a highly flexible catheter, so ultrasonic fluid transmission may be practical. Ultrasonic transmission in mercury is used for time-delay and information storage in the electronics and computer field. Aside from an abortive experiment with

mercury, we have not tested this method. The possibility of producing mercury poisoning incident to the great capacity of ultrasonic energy to atomize, vaporize, and emulsify was felt to be too hazardous. The conversion of the energy of the fluid wave into vibration of a drill tip has been discussed under *D. Longitudinal vibration.*

C. *Ultrasonic transmission through wires in ureter to calculus.* Compressional waves at high ultrasonic frequency are well transmitted in metallic bars. They have been employed, for example, as time-delay lines. Transmission of low frequency, useful power to a tool through long thin wires, roughly of the dimensions of the ureteral catheter, has not been developed. The applications are in the low intensity level, signal range, where transmission of barely detectable sound to a microphone is required.

We have not thoroughly explored the questions of what kind of metal, drawn into how many wires, of what cross section and temper would best fulfill our purpose. Our cursory examination of these questions was aimed at obtaining a useful, immediate solution, rather than the best. It was hoped that promising results would stimulate industry to expend the requisite time and money more successfully than have our queries. The later section on *Flexibility* will relate some of our findings on these questions.

Ultrasound is attenuated in a metal as it is propagated within it. Low ultrasonic frequencies are attenuated like X-rays in accordance with an exponential law.[25] The attenuation rate represents the fraction of the sound power dissipated along unit length of the material. For our purposes, we require a metal with a low effective attenuation rate, since for a desired output of ultrasound at the drill we wish to minimize our input of ultrasound and its conversion into heat within the body. We have found the attenuation rates that can be computed from available data[26] are only rough aids, since thin, flexible wires held loosely in catheters convert a large and variable portion of their initially imparted longitudinal vibration into transverse (i.e., flexural) vibration, there being considerable coupling between these two modes of vibration. The factors determining the actual degree of coupling between the two modes of vibration can be listed, but we do not have a precise formulation of their impact. Certainly the thinner the wire, the greater the coupling between the two kinds of vibration. This coupling would be of less importance if the energy stored in the flexural mode were available at the end of the wire for drilling, but unfortunately a large portion of the energy coupled into flexural vibration is damped out by the catheter. If this were not so, one would expect some level of dynamic equilibrium between the two modes of vibration, instead of the steady drainage of compressional energy into the absorbed flexural waves.

Young's modulus,* the coefficient of compressibility of a metal, should not enter into the degree of vibration coupling in the wire at a particular point. Since the ultrasonic energy stored in a wire during compression should be an important determinant of its drilling efficiency and since Young's modulus determines the force stored during compression, other factors aside, we should prefer a metal with a high Young's modulus.

The Q of a metal† is independent of frequency in our range of interest and is inversely proportional to the product, attenuation rate × velocity of sound transmission. On this basis, we would prefer a metal with a high Q and a high Young's modulus, since the range of velocity of sound in metals is narrow.

The result of the exponential attenuation of ultrasound with the distance it travels is that the relative importance of a high Q as compared to a high Young's modulus shifts, depending on the actual attenuation (length of wire and attenuation rate). Such a situation might imply a different optimal choice of metals for different circumstances. Fortunately, we have found that the optimum is unnecessary since the limitations on the method developed are not stringent; other considerations then become paramount. Because the impact of coupling between compression and flexion is not easily appraised in combination with the other factors listed and still others to be related, we have had to depend primarily on empirical observations, often on materials not strictly comparable, nor perhaps even characteristic of the better results that the metals they represented might have yielded.

An important clinical need is that the wire be as flexible as possible. Since the flexibility of a wire is inversely proportional to Young's modulus, we see antagonism between flexibility and good energy storage. We also seek a metal which will not break under the enormous cyclic stresses induced by ultrasound. Some metals fatigue (crystallize and break) when subjected to much repeated stress. We have tried steel piano wire, iron, aluminum, copper, brass, and monel. Monel is definitely superior to all, although possibly tungsten, expensive and not freely obtainable, or a recommended magnesium-manganese-aluminum alloy which we could not solder, might have been useful. We concluded that, except for poor flexibility, monel, easily soldered and with wide availability, low attenuation rate, and large Young's modulus, was superior to the other metals we tentatively

* Young's modulus is one hundred times the force required, per unit cross section, to compress the material one per cent of its length.

† Q is an index of the augmentation in response of a metal to resonant vibration; it will not be defined here more precisely.

considered;[8] the differences in flexibility resulting from inherent differences in Young's modulus among the metals were far outweighed by the fact that the flexibility of a round wire decreases as the cube of its diameter.

The questions of what kind and temper of monel and the number, size, length, and shape of the monel wire sound conductors will be considered later, after the source of the sound has been discussed, since clinical factors will be importantly involved.

D. *Ultrasonic drilling requirements at the calculus.* Drilling with low frequency ultrasound from a magnetostrictive source is rapidly coming into use in industry for hard materials (ceramics, tungsten carbide) or non-round holes. The drill vibrates in the direction to be penetrated and operates in a circulating water slurry of finely powdered abrasives, such as boron or silicon carbide. Teeth, in the preparation of inlays, are drilled similarly, using a hand-held transducer. Penetration of the drill with little wear depends on a high amplitude of motion. At least 0.001" peak-to-peak excursion (25μ) is desirable; larger values are obtained and cavitation* may be an important factor. It appears that cutting is accomplished, not by the tool, but by the fine particles of water-suspended abrasive impelled by the ultrasonic vibration of the tool with tremendous velocity into the work surface. The slurry also cools and removes drilling debris.

We found that the problem of drilling urinary calculi is fundamentally different from the dental and industrial applications, where very hard substances are to be drilled rapidly. Time, within reasonable limits, is not a therapeutically important factor in lithotresis. And urinary calculi are not particularly hard by comparison with teeth or the materials bored ultrasonically in industry; also, they often have a lamellated rather than homogeneous structure[23] and frequently fragment or shatter easily when ultrasonically drilled. Urinary stones, wet or irrigated with water, were drilled well with ultrasound without exogenous abrasive. We get the impression that fragments of the stone may themselves act as an abrasive and facilitate drilling. In any event, we have not supplied an abrasive in our studies, but it may well be that an innocuous one which does not provide nuclei for new stones and is otherwise harmless and well excreted may subsequently prove of value. Such an abrasive might speed drilling, or permit the use of a more flexible and finer catheter or require less ultrasound. But at this time, employing an abrasive seems an unnecessary complication.

* Cavitation is the sudden appearance of cavities in a fluid as a result of internal disruptive stresses exceeding cohesive forces, which are minimal when infinitesimal gas bubbles are present in the fluid.

Speedy drilling with ultrasound depends to a considerable extent on the amplitude of vibration, which for fixed energy increases with declining frequency. On the other hand, the number of drilling strokes per second declines with falling frequency, so that the frequency must not be too low. It should be at least above the audible range of 15,000 cycles per second so as not to be noisy. It is likely that energy levels should be sufficient to produce cavitation. However, although drilling of our calculi is suddenly very much faster when some minimum amplitude is reached, we are not sure that this transition corresponds to cavitation. It may well be involved in the variable rate of drilling in our experiments in cadavers.

SOURCE OF ULTRASOUND

Since low ultrasonic frequencies above 15 kilocycles are desired, sources capable of producing energy in wires in this range need to be considered. Whistles and sirens can be neglected, since they produce sound in non-solid media which couple poorly to solids. The ceramic, barium titanate, and magnetostriction are the two sources of ultrasound we tested. Both of them produce ultrasound of too low an amplitude to permit satisfactory drilling so that a mechanical transformer is coupled between the source of the ultrasound and the wire sound conduit going to the calculus, thereby increasing the amplitude of the vibration while reducing the area through which it passes. The transformer is a solid metal horn (cone) designed to resonate mechanically along its axis, the two ends vibrating vigorously to and from a nodal, pressure-stressed plane near its middle. The amplitude of the ultrasound is multiplied in this way by the ratio of the end diameters of the cone. The taper of the cone is best exponential* but a straight taper is quite satisfactory. We have tested both.

BARIUM TITANATE

Barium titanate with 4 per cent lead titanate is a newly developed ceramic material with unusually large changes in size (1 part in 10,000) under the influence of differences in electrical potential, provided it is polarized by being subjected to a high steady voltage (more than 30 kilovolts per inch while cooling through its Curie point (120° C.). If the titanate is permitted to reheat, it loses its responsiveness and must be re-polarized. We have found this characteristic a drawback in experimentation.

* The cross section decreases by a fixed fraction per unit length along the axis of the exponential cone.

For efficient energy transfer, the transducer must be excited electrically at its mechanical resonance. For a low ultrasonic frequency, a barium titanate rod needs to be almost four inches long, which would require impractically high voltages if the two ends were to be electrically excited. However, Mason and Wick[27] have shown that radical excitation of a hollow tube will effectively induce low frequency resonant oscillation of the tube along its axis about its midpoint. We made an instrument modified somewhat from Mason and Wick's* design. They report peak-to-peak excursion at the tip of their cone of 0.002" with only 6 watts input power at 18 kilocycles. While this device was quite capable of excellent drilling at the cone tip, we found it did not transmit enough energy through a wire in a catheter for satisfactory drilling at its tip. No doubt this method could have been improved; we discontinued using it because commercial magnetostrictive tools were found to be satisfactory without further development. This transducer may well be of value particularly for dental or bladder stone drilling.

Another way of coupling barium titanate to a horn for ultrasonic drilling was employed for us by the Brush Company. A barium titanate plate soldered to the base of the cone was excited in the axial direction at its resonant frequency, which was designed to be the third harmonic of the horn. Like the resonant barium titanate cylinder, this device did not have sufficient power for consistent remote drilling. Such a design is inherently wasteful of input power and seems to us of less interest for a future application to lithotresis than the resonant, radially excited tube.

MAGNETOSTRICTION

At present, industrial ultrasonic tools depend on the change in length of certain metals, especially iron, nickel, and their alloys, when they are permeated by a magnetic field. The change in length is very small, about 30 parts per million for nickel. A rod of nickel can be made to vibrate in length about its midpoint like the titanate tube by winding a coil of wire around it through which flows alternating current at the mechanically resonant frequency of the rod, along with direct current to provide a basic level of polarizing magnetism. At resonance, the amplitude of vibration considerably exceeds the static, 30 parts per million, magnetostrictive effect, the amount depending on the Q of the metal and its loading. The high fatigue resistance of nickel and its alloy makes them well suited to this purpose; the nickel-copper alloy, monel, is excellent for fabricating the horn

* We wish to thank Dr. Mason and Dr. Wick for their kind helpfulness and advice.

to amplify the sound density. In practice, laminated magnetostrictive metal in the form of a rectangular O is excited by two solenoids on the long arms of the O, since in this way the magnetic circuit is highly efficient. The resonant horn is screwed tightly to a short side of the O which vibrates lengthwise about nodes at the center of its long sides, where it can be clamped for support without loss of power. Water cooling is common. The frequency of the ultrasound is usually 25 to 30 kilocycles, with adjustment for actual resonance. Our most satisfactory results have been obtained with a commercial transducer activated by a generator of 500 watts power, of which we use only a fraction, for reasons to be discussed below.

III. ADAPTATION OF ULTRASONIC DRILLING TO LITHOTRESIS

Our studies finally lead us to choose an industrial source of ultrasound of high intensity at 25 kc. available at the tip of a monel cone to be transmitted via monel wire through the urethra, bladder, and ureter to the calculus, which was to be bored in the presence of water but without exogenous abrasive.

PLASTER MODEL OF URETER

We recognized that success or failure in animal experimentation might not signify the same outcome in man, since we found that drilling by a wire in a catheter was markedly influenced by the curvatures of the catheter: when straight, the wire drilled best. Furthermore, the dimensions are quite important; scaling from dog to man is not warranted, the length and lumen of the dog's urinary tract being considerably less than man's. A large sheep is comparable in weight to man, but we had no facilities for handling this animal. Instead, we made a bivalved plaster cast about a catheter within a ureter in a cadaver so that we could hold a catheter as though it were in a ureter. This expedient neglected the mobility of the living ureter (1½"-2" according to MacAlpine[28]), which would have ameliorated the unyielding, sharp plaster curves imposed by the model on the wire-containing catheter.

PULSATION

This model demonstrated vividly that considerable heat is generated wherever the wire conducting ultrasound is pressed against a rigid structure, such as the catheter at a sharp curve. Accordingly, since drilling requires a high amplitude, the obvious solution for excessive heat is to pulse the ultrasound so that the *average* heat produced does not overtax the cooling capacity of the circulating blood and thereby cause an untoward

rise in temperature. Empirically, we have settled on a cycling time of half a second on and half a second off.*

BARE OR SHEATHED WIRE

Implicit in our study is the idea that the ultrasound wire would pass through a catheter. Yet we realize that wire bare within the ureter may finally be preferable. Other factors equal, bare wire has the advantage that, for a given lumen of ureter, much more ultrasound can be transmitted if its whole lumen is filled with the ultrasonic conductor. Pulsation can avoid excessive temperature rise and heat production may be less with wire pressing against resilient tissue than against firm catheter. However, two reasons deter us from this approach, preferable as it may ultimately be. One is that our wires sometimes break while conducting ultrasound. Since we do not know how to avoid fracture of the metal, the risk to a patient of a bare broken wire might not be avoidable if the drill-wire were unsheathed. Furthermore, not knowing at what intensity low frequency ultrasound may prove harmful to the body, it was better to insulate the ureter in good part from ultrasound by means of the intervening catheter. In our development, this seemed preferable to conducting a biological determination of the harmlessness of ultrasound through a wide range of intensities when we did not yet know our requirements. The plaster model demonstrated to us that it was possible to transmit sufficient ultrasound through a monel wire within a catheter to drill a urinary stone, even when the catheter was filled with water, as it probably would be in any clinical application. However, drilling efficiency, as one would expect, fell somewhat when water instead of air surrounded the wire. The water, being viscous, damps the movements of the wire.

FLEXIBILITY

A single flexible wire to transmit ultrasound was our first objective, yet for other reasons monel, a fairly rigid metal alloy, was finally chosen. Too stiff a device pulls too much at the attachments of the ureter, although it is surprising how much traction these tissues will stand. Mellick regards four

* However, this subject requires separate exploration. We have obtained an impression not yet put to test that frequent cycling with the *same* fraction of drilling time may drill better than slow cycling. Such a circumstance might be explained by our noting that there is an optimal drilling force for a given condition (curvature, power, stone type, etc.) of drilling and each period with power on will send the drill twice through the optimal condition, provided the actual drill force is optimal for less than the steady power level.

pounds as a reasonably safe limit for traction on a looped catheter engaged on an impacted ureteral stone.[29b]

Another difficulty caused by a stiff wire drill is not at first apparent. Over and over in our bivalved plaster model, a 19 mil wire (1 mil is 0.001 inch) emerging from the tip of a catheter would bypass a stone placed in the groove representing the ureter. Vibration can markedly diminish friction,* not only by substituting lower sliding friction for starting friction, but by reducing the force of friction at each oscillation to zero. With ultrasound, the drill tip is out of contact with the work surface at least part of each cycle, and then there is no friction. If the side of the drill is not held, as by a hole already started, so it can move sideways, it rapidly deflects across the hard surface to be drilled, deflecting components being highly likely when a drill first makes contact with a surface. Of course a stiff wire bent into a curve by a catheter in our plaster mold or in a ureter starts with a considerable deflecting component. Even though increased flexibility does not eliminate this tendency of the drill-wire to bypass the stone,† it is an important step towards this objective.

TEMPER

Our monel wire was cold drawn, which is essentially spring temper. Wire, whether soft or spring temper, has practically the same stiffness up to the elastic limit. However, once past its yield point, the soft wire opposes bending little more, unlike the spring wire at this amount of bending; the spring wire progressively increases its opposition to bending until it, too, reaches its yield point. We tried annealed monel wire in comparison to cold drawn but did not find any significant difference. The spring wire by comparison was easier to obtain and handle, did not take on so many bends, and could be pushed more easily into our catheters when held in the curves of the ureter. We also suspect that the higher yield limit of the spring wire permits greater levels of ultrasonic intensity without breakage and with less attenuation. We regard the question of metal temper as still open; we did not find a large difference which would have prompted an extension of our study of this problem. Although we now use spring-temper metal, so-called "stress relieved" spring wire should have less attenuation and be less subject to fracture.

---

* In jet planes, which vibrate much less than propellor-driven ones, a vibrator has to be incorporated in the instrument panel to make the instruments read dead-beat.

† The tendency we allude to is hard to describe in a single word; among ourselves we called it "goofing," as though the wire behaved in a silly, irrational way when it "refused" to drill. We shall call it "skewing" and later we shall discuss its suggested therapeutic applications.

Multiple fine wires. The fact that stiffness of a wire depends on the cube of its radius permits multiple wires in the same catheter lumen to transmit ultrasound with considerable increase in flexibility. However, increasing the flexibility of a wire increases the attenuation of longitudinal ultrasound in it by increasing the coupling of this mode of vibration with the wasteful flexion vibration already described. In addition, there is more contact between vibrating metal surface and catheter wall with multiple wires than with a single large one, which also increases transmission loss. In case of breakage the important clinical advantage of many wires over one has been mentioned. Our experiments with multiple monel wires finer than 19 mils diameter, namely 6, 8 and 11 mils, were not encouraging. Useful drilling energy was rapidly lost along the course of the catheter. Fine braided wire became incandescent and burnt at the cone. The 19 mil wire was the finest round wire we tested which transmitted ultrasound well. Possibly one of a size between it and 11 mils, our next smaller, might have had advantages, particularly since multiple strands of 19 mil wire were stiffer than we desired. Perhaps again, as in the choice of metal, the optimum size and number of wires may vary with the length and the curvatures and tightness and lumen of the ensheathing catheter, since attenuation is exponential and what is tolerable for short distances or with mild curves may be impractical for long distance or with sharp curves. Certainly, irrespective of configuration and shape, more wires will be more flexible than fewer ones occupying the same space and so we next consider shape and configuration.

Ribbon wire. In electrical technology, a very flexible conductor to a rotating galvanometer coil, for example, is obtained by using many fine, loose wires of a ribbon shape, like tinsel. A flat, metal ribbon bends freely, curving like a watch spring, since the stiffness of a rectangular beam increases with the square of its thickness measured in the direction of bending, while increasing only proportionally with its width. For a fixed cross section, any desired degree of flexibility can be obtained in one direction by sacrificing flexibility in the other. If the ribbon is free to twist, flexing it in a direction which is not optimal will not meet with seriously increased stiffness, since the ribbon will twist so as to bend almost in the best way.

We tested monel ribbons passed through ureteral catheters as conductors of ultrasound. Our first experiments were on ribbon of 3/64″ x 0.004″ of cross section equivalent to 15.4 mil diameter roundwire. The sound was poorly transmitted and the ribbon broke frequently at the intensity of ultrasound required. Whether the ratio of width to thickness was too extreme, or the cross section was too small, or the ribbon in being drawn had retained stresses which predisposed it to early fatigue, we do not know.

Our impression was that the flexural mode of vibration was absorbing most of the ultrasound and that a less extreme application of the ribbon theory was desirable. The second trial was much more successful, the ribbon being 1/32" x 0.010", the same cross section as 19.1 mil round wire. This size and shape wire proved satisfactory, although in great likelihood it is not the optimum. It is a flexible, effective conductor of ultrasound within standard ureteral catheters.

An important advantage of ribbon over round wire results from its behavior in water. The damping effect of a fluid on the compressional vibration in a wire should be proportional to its viscosity, the amplitude of vibration, and the surface area of the wire. The ribbon will, for the same cross section, have more surface area than the round wire. However, although in water the ribbon is quite flexible when bending slowly, a property important for its application in a ureter, its flexural stiffness in water to transverse vibrating ultrasound will be considerably enhanced by its augmented surface and the high impedance of water to the rapid motions of ultrasound.* The result is that the ribbon in a catheter in our tests transmitted ultrasound better as a result of water immersion, the dissipation of the compressional sound through coupling to flexion being diminished so much as to exceed the simple damping losses due to the viscosity of the water. By a skillful choice of the right shape, it might well be possible to find a ribbon which, when immersed, has no preferential direction of ultrasonic flexion, unlike its action in air.

Coiled wire and ribbon. Flexibility can be obtained for a given wire by effectively lengthening it for the given distance to be transversed; the bending per unit effective distance is thus reduced. The classical way to accomplish this is the spirally wound spring.

Early in our studies, we wound our 19 mil round monel wire into a helix and found high attenuation with considerable heat production and poor drilling. As a result, we did not consider this possibility seriously until very recently, when certain basic facts concerning the effect on the transmission of audible sound in air through tubes and horns seemed inconsistent with our early finding. Accordingly, we have started to restudy the transmission of ultrasound in monel wire and ribbon wound into a coil, one end starting in the cone, the other being used for drilling. We have obtained highly variable results as yet not understood. We have found that a coil will not transmit ultrasound well if its turns are in contact, if the turns are too tight, if they are in direct contact with tissue, or if two coils are wound

* A whip can easily be bent but not snapped under water.

coaxially and touching each other. Although breakage of the wire seems to be reduced when it is wound into a coil, transmission of ultrasound and breakage itself vary unpredictably. Stress-relieved helices may prove superior to those without this treatment.

A ribbon helix, compared to a round wire helix, offers more flexibility and cross section of the conducting wire, and a shorter actual length for the required effective length, although having more surface area. In an attempt to avoid the hazards of breakage of an exposed wire, we molded a monel wire into a rubber latex bougie but found that the rubber became extremely hot so we concluded that the wire must be bare.

In the case of the external helix, this meant that the ureter itself would have to be exposed throughout its length directly to the ultrasonic shearing waves generated by the considerably longer coiled wire. By contrast, the free straight ribbons within the lumen of a catheter convey much less energy to the tissues, being shorter than the coiled wire and enclosed by the thick-walled catheter with which they are in poor acoustic contact.

If the variability of ultrasonic transmission by coils is mastered and controlled, a coil of ribbon, perhaps wound on an oval mandril to minimize friction, may be flexible, effective, and superior to the ultrasonic conductors we employ when passed through the catheter.

ATTACHMENT OF WIRES TO CONE

The design of the ultrasonic transducer rests on the benefits realized in exciting a mechanical system near resonance. When there is a change in impedance to vibration, a transmission loss ensues with reflection backward of part of the incident energy. By making the necessary impedance changes in the system at anti-nodal points a half-wave length apart, where particle velocity is greatest and pressure changes least, any ultrasound not transmitted at the connection is reflected back to augment the vibration of the element, and stress is least. That is why the wires are soldered into a small hole at the tip of the cone at an anti-node. Elsewhere, the solder would not be strong enough to hold them.

At first, we followed industrial practice and used the lowest temperature silver solder* to make this connection. Later, we obtained the impression that the local heating of the monel wire, despite its excellent heat resistance, was partially responsible for the frequent breakage just beyond the soldered joint. Accordingly, and because we do not use full ultrasonic power, we find

* Easy-Flo of Handy & Harman.

50-50 lead-tin solder holds the lithotresis wires in the cone as well as the silver solder and melts at a much lower temperature.

Earlier in our work, we used a tapered collet to hold a single wire, tightening it by threading a nut on tapered threads near its base. While successful for a time (wear occurred in the collet, probably because of occasional ultrasonic slippage) and perhaps a prototype for a clinical application, it lacked the versatility of a soldered joint in which different sizes, numbers, and shapes of wires could be accommodated.

Surprisingly, a wire inserted in a coaxial hole at the tip of the cone energized by our low power barium titanate transducer was held very well by a small set screw. Whether it can transmit effectively higher intensities of ultrasound has not been determined.

LENGTH OF WIRE

When ultrasound is transmitted to the resonant cone, very little is lost to the surrounding air because of the marked difference in the acoustic impedance of air and metal. If the cone tip carries no tool, most of the energy is reflected back to form standing waves in the cone and transducer, instead of the travelling waves which would have resulted if the cone were tapered smoothly to connect with an endless monel bar. Standing waves are the result of two sets of waves reinforcing each other and travelling in opposite directions. The waves children make in a jump-rope when one end is tied to a post are standing transverse waves. The waves of the wake of a ship are an example of travelling waves. Every particle in a wire through which a steady train of travelling longitudinal waves passes is subjected to compression and rarefaction and to high velocity. In contrast, where the steady waves are standing, each point varies in the proportion between pressure changes and velocity changes; the nodes are pressure-change points, the anti-nodes being velocity-change points, and the size of the changes due to the reinforcement are greater than in pure travelling waves. Ultrasonic drilling depends on high velocity so that ideally it would appear that a long drill wire should be of such a length that it is a resonant system, an integral number of half-wave lengths from cone to drill tip, which would give best reflection at its end. In this way, the full benefits of the standing wave should be realized.

Empirically, we have changed progressively the length of our conducting wire while observing drilling effectiveness. To our surprise, good drilling did not require a critical length.* Instead, there were critical lengths (per-

* It is possible that a more careful control of length would reduce the tendency to wire breakage near the cone, by reducing the stresses there.

haps representing anti-resonance) at which drilling did not occur, but with chance lengths of wire failure to drill occurs rarely. Our explanation is that the required resonant frequency need not be very precisely adjusted; the cone and transducer do not match each other perfectly; and the Q of the whole operating system not being extremely high (see Mason and Wick's measurement of the effect of frequency on amplitude),[27] a minor shift in frequency and consequent change in half wave-length in the wire (about 4″) usually suffice to bring it close to the optimal integral number of half wave-lengths so that the drill vibrates with sufficient amplitude.* Also, when the drill is pressed against the stone, it causes a shift in phase of the ultrasound reflected at the tip; the optimal frequency for the loaded system is thereby shifted away from that for free resonance. This factor may also aid in obtaining drilling without too critical a length.

Catheters for the ureter are a standard 28″ long and we have made our sonic conductors long enough to extend from the cone, with a few inches to spare, through the whole catheter. Actually, the optimal condition for drilling a particular ureteral calculus would be a conductor as many integral half-wave lengths long as will reach it easily, but no longer, so that no energy is wasted. Any length chosen at random should always be tested to make sure that it drills effectively—that it is not the critically wrong length.

ARTIFICIAL URETERAL CALCULI

We found it very difficult to insert real urinary calculi into the ureter of a cadaver through the renal pelvis or a ureterotomy, even after preliminary dilation of the ureter with a bladder on a catheter: a stone small enough to be insertable was not the prototype of one requiring operative or manipulative ministration; rather, it represented those which pass spontaneously.

At first through a small ureterotomy, but latterly through a calyx of the split kidney, we have passed a polyethylene cannula down the ureter to the site of the prospective calculus. We have then injected plaster-of-Paris, holding the ureter with the fingers (no clamp seemed as good) so as to form a plaster "stone" in the ureter. Sesame oil, injected prior to the plaster through a different catheter, prevented the plaster from extracting water from the mucosa and damaging it. The best holder for the plaster was found to be the tin collapsible and disposable medicament tube (toothpaste tube). It was easy to fill at its open end and fitted the polyethylene tube via a rectal nozzle screwed onto the narrow end.

* Tuning for resonance has been by ear, since, at resonance, cavitation of the cooling water in the transducer is noisy and loudest.

A dental variety of plaster* sets quite hard within 20 minutes and has a pasty consistency right from the start. Compared to urinary calculi, it drills somewhat less readily and, being highly homogeneous unlike the laminated and variably composed urinary calculus, it is less likely to be disrupted by ultrasonic drilling. Weighting the scales somewhat against the artificial stone makes it an acceptable, adaptable substitute for real urinary calculi.

DRILL TIP

Another step towards the objective of avoiding skewing of the ultrasonic bit was the redesign of the drill tip, starting from the simplest solid form. When we shifted from single to multiple round wires, our drill tip consisted of these wires hard-soldered together. The solder wears away slowly in drilling and the hard kind therefore seemed preferable to soft. This type of solid tip drilled our wet clay tile† rapidly in our tests but, when tested in animals and in cadavers, perforation of the ureter sometimes occurred and skewing could not be prevented unless manual manipulation kept the drill tip on the face of the stone. Once a hole is started, its sides keep the drill from skewing, so the problem is to initiate the hole properly.

In retrospect, the proper redesign of the drill tip seems obvious, but we tried various shapes of solid tips with poor results. Sound was badly transmitted to the tip, as would be expected when its mass was considerably different from that of the wires (impedance mismatch).

A hollow tube soldered onto the wires has many advantages over a solid one as a drill tip. At present, we use a monel tube (no. 10, i.e., 3.2 mm. O.D.) between 3 and 5 mm. long, soft-soldered to four 1/32″ x 0.010″ spring temper monel ribbons, disposed in diametrically opposite pairs (Fig. 2); or, perhaps better (not yet adequately tested), each ribbon is separately soldered to the inside of the tube, one to a quadrant. Spot welding may be superior, particularly for clinical use, since it would probably be more dependable than solder. Very little solder is now used to avoid filling the lumen and to avoid lengthwise variation in lumen size or shape. Otherwise, the debris from the stone impacts within the drill because it is then not self-cleaning.

The hollow drill, even when energized along only two opposite elements, drills well and uniformly about its entire circumference. It has relatively low mass and low drilling area, so that the intensity of ultrasound per unit

* Stonehard Speedrock (Baker & Co.) fabricated for casting inlays.

† Our test drilling material was a 5 mm. thick, flat, baked Jersey clay tile of roughly the same drilling resistance as urinary calculi. We are grateful to Roberta Leber for making them for us.

of drilling surface is high. After all, our primary interest is in disrupting the urinary calculus and a hollow drill has the virtue of proceeding efficiently to this goal, since it tends to fragment the inner, undrilled core without wasting ultrasound on grinding each particle.

The drilling force needed is, of course, related to the drilling area. By having a smaller drill surface for a given size hole, the hollow drill requires proportionately less drilling force, an important consequence discussed below.

The hollow drill, if pressed against a stone so that opposite lips engage, does not skew: the deflecting tendency of one side is opposed by that of the other and the small convexity of the calculus lodged in the cavity of the drill acts as a guide and prevents deflection, so long as there is any drilling force. Clearly, the larger the diameter of the drill, the more likely it is to engage *both* lips and not to skew—and the larger the hole it bores.

A large hollow drill, even while activated by ultrasound, is very much less likely to perforate the ureter than a smaller one. In cadaver experiments, our large no. 10 drill has not perforated the ureter while vibrating ultrasonically and while allowed to press against it steadily in one case for fourteen minutes.

If the ribbons were soldered together into a drill tip, its surface contour would be fairly streamlined. Should such a drill bypass the stone, retraction would be unimpeded. However, the hollow drill, particularly when it is connected within to the four ribbons disposed in two opposite pairs, is something of a hook. Such a hook, if it engages the stone on withdrawal, can be used to remove the stone by traction on the connecting wires, without further ultrasound, following the classical methods of the bypassing catheter, basket, or loop already mentioned. Here the rôle of ultrasound would have been to drill alongside the calculus, promoting easy bypassing either by grooving the stone or merely by the anti-friction effects alone of ultrasound. Alternatively, we have found in the cadaver that a bypassed stone can also be drilled backwards, a single lip of the tubular drill on the catheter side becoming the active drill edge, as slight tension is put on the ribbons to pull the drill back towards the bladder. In this way, it is easy to bring the drill back to the catheter, if it is so desired, and drilling can be resumed elsewhere on the calculus, this cycle being repeated until the residue is small enough to be excreted spontaneously.

If the drill is held fast in a drill hole within the stone, as is sometimes the fact when ultrasound is stopped, it can be utilized for traction in the classical manner or can be released readily by resuming ultrasound while withdrawing the drill with gentle traction (50 grams).

To remove the drill from the ureter, it is always preferable to pull the ribbons first, with moderate ultrasound on, so that the base of the drill tip is seated on the somewhat larger (no. 11 as compared to no. 10) catheter. Then the assembly is easily withdrawn without harm.

Of course, the larger the cross section of an instrument, the more difficult and hazardous it is to pass up the ureter and the more cases in which it becomes inapplicable. MacAlpine, in his monograph *Cystoscopy and urography,*[25] states that the living ureter is quite distensible and that successive passage of progressively larger catheters easily permits entry of a no. 11 catheter. He refers to others who dilate considerably further. Local ureteral dilation to a greater extent is also referred to, as by Bransford Lewis to no. 24 and Dourmashkin to no. 20. McCarthy reports dilation to between no. 16 and no. 18.[28]

For these several reasons we have concluded, especially in early work, that a large no. 10 hollow drill tip, smaller than the lumen of the no. 11 catheter which carries the ultrasound-conducting metal ribbons, was preferable to a smaller drill tip which could be threaded through the catheter after it was once in place. Specially thin-walled, nylon woven catheters were tried but the gain in lumen-size was not great, about half a unit in French size, and they were discarded for another reason. Polyethylene catheters were found to damp ultrasound excessively. Perhaps the sheath made of stainless steel coiled ribbon, as used in cystoscopic forceps and scissors and in the Morton basket, with its considerable flexibility and proportionately large lumen, will prove superior to the plastic-impregnated woven nylon catheters we use (one is being made for trial) and may ultimately permit substitution of a withdrawable drill.*

Should our no. 10 drill tip, an uncompromising right-circular cylinder seated on an open-end no. 11 catheter, be too extreme for harmless passage through the living ureter, possibly a rounded wax tip molded onto the tubular drill, but easily drilled away, may facilitate its insertion. Low level ultrasound, we have found, considerably reduces the friction between objects which are to slide over one another. A drill which jams snugly inside a catheter can be passed through it with ultrasound. To some extent, this statement also applies to the drill tip at the end of the catheter bare within the ureter of the cadaver; we expect it will also apply to the living

* The delivered spiral wire catheter has a larger lumen than the no. 11 we used, is quite flexible, and at the 4¼" drilling end is no. 9. It grips the ureter very well at 300 mm.Hg. suction. Interestingly, Benjamin Franklin first proposed this catheter design (Pepper, William. *The medical side of Benjamin Franklin.* Philadelphia, William J. Campbell, 1911. pp. 28-29). See Figure 1. We are grateful to Miss Elizabeth Thomson for bringing this reference to our attention.

ureter. That is why we also hope the large no. 10 drill tip will be more easily passable with ultrasonic assistance than might seem reasonable from the urologist's experience.

In fact, we cannot help pointing out that ultrasonic activation of catheters, perhaps made of coil-wound metal ribbon, may well facilitate their passage up the ureter, an application of ultrasound quite distinct from lithotresis.

DRILLING FORCE

The natural way to provide drilling force is to press the drill against the work. However, our drill is inaccessible and attached to four flexible metal ribbons about 30″ long lying loose in a catheter and terminating in a 12½ pound transducer to which a heavy electrical cable and two water tubes are connected. To move this assembly delicately, while possible, is not necessary.

We concluded, and verified experimentally, that drilling force is quantitatively transmitted to the drill tip when the catheter is pulled towards the cone along the vibrating ultrasonic ribbons, provided that there is some curvature of the catheter outside the body. Such a method does not move the catheter in the ureter, if the traction applied is less than the starting friction between catheter and ureter, or if the catheter is held at the urethra or in the bladder so as to prevent motion.

There is an optimum drilling force for any given arrangement of catheter bore and curvature, drill size and shape, flexibility and size of ultrasonic conductors, intensity of ultrasound, etc. If too much drilling force is applied, the overloaded drill does not leave the work and drills poorly. Under too little force, the drill does not advance because it fails to hit the work itself or to throw water and/or abrasive at the work. The tendency, where measured force is not utilized, is to drill with too much force. In a cadaver, we drill well with an effective force between 100 and 150 grams, of which 50 to 100 grams is applied towards the axis of the cone with a spring balance attached to the catheter at its end.* Every effort is made to avoid angulation of the small length of exposed ribbons between cone and catheter to minimize their breakage in this critical zone.

The curves of the catheter and the tightness of fit of the ribbons in it are important factors in determining optimal drill force and efficiency of ultrasonic transmission. If the ribbons fit too loosely in the catheter, breakage and perhaps attenuation may be enhanced. (This aspect is not important, since the therapeutic tendency to use the smallest catheter is in the opposite

* In a subsequent section, the source and use of internal drilling force are discussed.

direction.) If the ribbons are snug, attenuation is augmented, primarily where the curves are sharpest. In this circumstance, only low drilling force is acceptable, since more increases the attenuation. The changes in drilling efficiency as a result of drilling force indicate the extreme range; within it, drilling force is fortunately not critical.

The four ribbons we finally chose to use are quite free in the lumen of the no. 11 catheter. They are sufficient to carry the requisite ultrasound, are not confined so as to give high attenuation in the curves encountered, and are not so few as to make loss of the drill tip at all likely due to sudden breakage of all the ribbons together within the catheter. Furthermore, they are not too stiff and do not fill the lumen of the drill tip to which they must be attached. Two pairs of ribbons lie on top of each other with minimal friction when mounted as described, yet transmit drilling force well without buckling (see Fig. 2).

A low drilling force is an important desideratum. The hollow drill contributes to achieving it. The possibility of damage to the ureter by the drill tip is reduced with lessened drill force, the likelihood of ribbon breakage is thereby minimized and so is the tendency to skew. Angulation between drill and stone and attenuation are reduced with less drilling force, since pushing on a wire tends to bend it.

DISCARDED METHODS TO ASSIST IN STARTING THE DRILL IN THE CENTER OF THE STONE

Two major factors in reducing the tendency of the drill to bypass the stone in the middle and upper third of the ureter in the cadaver were the avoidance of stiffness in the sheathed metal conductor of ultrasound and the development of the large hollow drill tip. A third, that the unopened abdomen with all the viscera intact permits less angulation of the ureter than the eviscerated cadaver, seems likely; examination of a cadaver with viscera intact showed the ureter with our catheter in place to be only slightly distorted, much less than in the empty abdomen. X-ray films of a no. 9 catheter in a living ureter with our ribbons in place confirm this impression.* Still, we found that angulation with bypassing of the stone was a problem in the cadaver and felt uncertain it would not be one in the patient. Many ideas to prevent this outcome were considered; some were tried. Several are outlined below to aid those who may wish to reconsider them.

* We are indebted to Dr. B. M. Harvard and Dr. Thomas Ray for making this observation.

Different types and kinds of bladders were attached to the end of the catheter which was made with a separate lumen in or along its wall to inflate them. One type was designed to center the catheter in a larger ureter at the site of the stone. Although it succeeded in doing this, it failed to prevent angulation immediately beyond it, where the stone was, and so was only slightly helpful. Another kind was designed to extend towards the stone, like a cup, but did not aid.

One set of methods was directed to bending the catheter towards the stone, so that angulation would occur elsewhere than at the drill-stone interface. The loop catheter was tried for this purpose but required a delicate manipulation: too much correction was as bad as too little. Wires of opposite spring in the catheter can be rotated together and with respect to each other to get as much spring in a given direction as desired, and the whole catheter can then be rotated *in situ* to orient the curvature as desired. In the cadaver, drilling without angulation and skewing could be accomplished by bending the drill wires optimally by hand. Again, the same objection applies. Although these methods might have been made effective, a more automatic one, requiring less skill in the clinic, was sought.

Anyone who has ever handled fine wire knows that stretching will straighten its bends. Would this not apply to the ureter? It did, when the ureter was pulled by an instrument.

Clinically, the catheter, with an external inflatable bladder, similar to those developed by Dourmashkin,[12] could be made to grip the ureter so that traction on the catheter would straighten the ureter. Bladders of rubber latex* with reinforcing longitudinal nylon threads to prevent blowout, were found to over-distend the ureter while providing sufficient traction and were discarded. Accommodation to distension is a characteristic of the ureter.[12]

An ideal catheter—we do not know how to achieve it—would be one which could be made remotely to open about the stone, like the petals of a tulip, so that the stone always became harmlessly centered in the petals without being bypassed and could be drilled without further ado.

TRACTION AND DRILLING FORCE BY MEANS OF SUCTION

Suction on the surface of the catheter gave releasable adhesion between catheter and ureter and permitted traction to be applied to the ureter to minimize angulation between stone and drill.

* Cargyle membrane is strong, thin, flexible, and inelastic. A single trial suggested it might be superior to rubber for ureteral bladders.

At first, a separate lumen and a tight, knitted cotton sleeve about the end of the catheter were tried. Through the interstices of the sleeve the reduced pressure was to be transmitted. The knitted cloth abraided the ureter, and too much wall space in the catheter was wasted on the extra lumen. Our previously fabricated, thin-walled catheters were found to collapse and leak sometimes under the vacuum and were therefore discarded.

Our present catheter is a single lumen no. 11 open-end type with many small holes for a distance of four inches, starting a quarter of an inch from the open end. Such a catheter, when supplied with a vacuum of about half an atmosphere, grips the ureter quite tightly and considerable traction can be applied without slipping. We have not seen slippage in a cadaver with less than 250 grams traction. Usually, much higher forces can be sustained. Traction on the ureter with forces of considerably less than 250 grams straightened out angulation between catheter and stone sufficiently for our purposes in most instances; clinically, where the closed abdomen and visceral attachments help, we estimate a force of 100 grams should be adequate. Traction has the desired virtue of being essentially automatic: too much suction or traction, instead of over-shooting the mark by promoting more angulation, only minimizes it still further.

When traction is applied to the ureter along with suction, even with the drill and catheter pushed up to the stone, the ureter stretches lengthwise and the drill tip usually needs to be advanced again within the ureter to meet the stone. It was found that drilling force alone was not always effective for this purpose because the suction in the catheter is communicated to the ureter just beyond it. The ureter tends to close down on the drill tip and may altogether envelope it, interposing itself between stone and drill. Since soft tissue is not drilled, no lithotresis can then occur. On the other hand, if the drill is properly in contact with the stone when suction is applied, then the ureter presses about the stone and the back of the drill, holding them together, providing drilling force and tending to prevent angulation.

The drill force resulting from suction is derived from the area of the whole lumen of the drill tube while the effective drilling surface is only the area of the rim of the tube wall. In this way, a useful drill-force of about 40 grams is realized to be added to any externally applied drilling force. It also has the advantages over external force that it does not promote bending and friction of the metallic ribbons.

Our method for avoiding skewing and angulation, where a stone is in the upper or middle third of the ureter—it does not appear to be a problem in the lower third—is to advance the catheter and drill to the stone but to

avoid pressing against it since that promotes angulation. Then without suction the catheter is pulled at the urethra, the external curve of the catheter to the cone being maintained, with a force of about 100 grams, which usually will not move it within the ureter but is enough in most cases to prevent angulation sufficiently between stone and drill so that proper drill-seating can occur. The drill is next advanced with a minimal drilling force with ultrasound on, pulsed half a second on and half a second off. When the drill ribbons stop moving into the catheter, after a few seconds suction is turned on. Now, in a clinical application, we would expect ultrasound and traction but not suction would be discontinued temporarily pending confirmation of good coaptation between drill and stone by X-ray. In our cadaver studies, direct visual confirmation is all that is required and, if stone and drill are properly in contact, drilling proceeds almost immediately with suction as the sole drilling force.

At this point, drilling is supposedly precarious because the drill tip is not yet seated deep in the calculus and skewing is still possible. Consequently, we drill for a minute or two with low internal 50 g. drilling force derived only from suction, and either no catheter-at-the-urethra traction or minimal traction, since the suction tends to fix drill and stone together. Where we depend on the visual appearance of the ureter in the cadaver, the clinician would depend on the X-ray film and previous lithotresis experience—as yet not available—to decide how much traction to use. It may well be that traction even at the start is always to be preferred.

After this brief initial period of low force drilling, traction on the external end of the catheter, near the cone, which determines transmitted drilling force, is initiated at about 80 grams. Again, we are not sure whether continued traction on the ureter at the urethra via the catheter would be clinically helpful here, angulation aside, by further straightening the catheter and ureter and thereby minimizing ultrasonic attenuation and perhaps still further reducing the possibility of skewing. We have not used it in our latest work in cadavers. It should be noted that the 80 g. drilling force is transmitted through the stone to the ureter in which it is impacted. This force thus tends to stretch the ureter below the stone in the direction from which the drill comes and, if the drill is properly started, should reduce angulation and the skewing tendency. Figure 3 shows the relationship between the forces involved.

Should the measured bare length of the wire between catheter and cone considerably decrease during drilling, suggesting considerable movement of the drill tip away from the catheter, we immediately interrupt the ultrasound to examine the appearance of the ureter. Clinically, of course, an

X-ray film would be taken. We have not infrequently erred by discontinuing ultrasonic drilling at this juncture, thinking bypassing of the stone had occurred, only to find this conclusion was premature. Possibly the ribbons realign themselves in the catheter or the ureter stretches to change the relation between catheter and ribbons. In any case, the X-ray would be used to control the progress as well as the initiation of lithotresis, as in any other ureteral manipulation.

We have not indicated how suction is maintained in the catheter, considering the fact that metal ribbons within it must not be constrained by a packing, if ultrasound is to be well transmitted. Although it is possible to

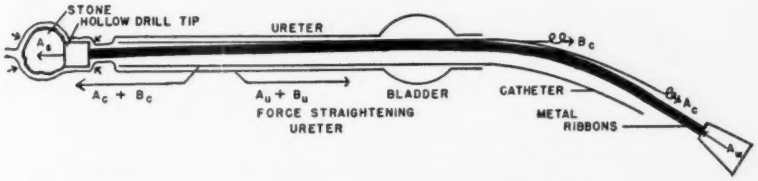


FIG. 3. Simplified, schematic diagram of forces involved in catheter gripping ureter by means of suction (source not shown) and containing wire ribbons ending in drill tip pressed against a ureteral calculus. The springs inserted in the arrows labelled B_C and A_C represent externally applied traction. The capital letter and the length of the arrow designate the magnitude of the force, the subscript indicates the structure on which the force acts. The stone receives from the drill tip via the metallic ribbons the external drilling force, A_S. In addition, the drill and stone are held together by the vacuum applied to the area of the drill lumen, represented by the small unlabelled arrows. The stretching force on the ureter ($A_U + B_U$) straightens it.

place the whole cone with the external curve of the catheter and means for providing drilling traction within a vacuum housing, having the packing at the catheter near the urethra, we have eschewed this solution as too bulky, heavy, and complex. Instead, we have used a vacuum pump capable of maintaining the low grade of vacuum we desire (half an atmosphere) in the face of a very large leak. We have had our no. 11 drill-catheters made with a single eye four inches from the external end and have fitted a small T-tube over it, with rubber seals at the ends of the top of the T, so that the side-arm applies suction through the eye to the lumen of the catheter. Since there is little flow from the ureter through the catheter, the vacuum in it from ureter to eye is essentially the same, the rise from half an atmosphere to full atmospheric pressure taking place entirely within the terminal four inches of the catheter. A 37 L./min. free air capacity high-vacuum pump with trap, provided with a gauge near the T connection, serves our purpose —a water pump was found to be inadequate. However, since capacity

rather than high vacuum is the desideratum, a smaller and simpler pump than ours would undoubtedly suffice (see Fig. 2).

It should be noted that in our studies suction for providing traction to avoid angulation was applied at first. Soon, the suction was found to be most helpful in supplying internal drilling force while fixing stone and drill together as the drill hole is started, if proper coaptation has been obtained. Traction to minimize angulation and permit good coaptation at the start now relies solely on friction between catheter and ureter. Later suction fixes the catheter in the ureter and permits as much ureteral traction as is desired.

IV. CADAVER EXPERIMENTS IN ULTRASONIC LITHOTRESIS

We have alluded frequently to our work in cadavers in discussing the various topics involved in lithotresis. The disadvantages of the open, and particularly the eviscerated, abdominal cavity of the cadaver have been indicated—primarily the increased mobility of the kidney, ureter, and bladder. The tissues of the cadavers were usually quite fresh but sometimes refrigerated and we found the dead ureter less amenable to catheterization than the live one. For this reason and since clinical urological practice in the passage of catheters the size of ours is well established (the effect of our unusual tip has already been discussed), we chose to pass our catheter by a simplified and effective nonclinical procedure.

A whistle-tip no. 5 ureteral catheter was threaded through the ureter either from the bladder or a renal calyx. Next a 19 mil round monel wire about six feet long was passed through its lumen. Advancing or retracting the catheter slightly aided this whenever any difficulty arose. Then, our special no. 11 catheter, empty, was threaded onto the renal end of the wire. Its leading end was a whistle-tip so as not to interfere later with the metal ribbons and to facilitate its own passage retrograde down the ureter. (Clinically, such a tip would be unnecessary.) This catheter was next threaded onto the no. 5 catheter as far as it would easily go. Now the renal end of the wire emerging from the no. 11 catheter was clamped, so it could not withdraw, and the other end of the wire, along with the no. 5 catheter from which it emerged, was pulled down. Some traction to straighten the ureter was maintained on the exposed large catheter. The wire and the two catheters moved together as a unit. By this means, it was surprisingly easy to thread our no. 11 catheter retrograde in the cadaver through the ureter to the bladder. Sometimes, a ureteral meatotomy facilitated its emergence into bladder and thence through the urethra.

To avoid drying of tissues and because the abdominal cavity must be regarded physically as filled with water rather than air, which reflects ultrasound, we partly filled the abdomen with water, after the drill ribbons had been passed retrograde through the special catheter which was then pulled down into the ureter, and after the artificial stone had been made.

We have found, in the cadaver and elsewhere, that drilling was best with enough water to sweep away debris from the drill. It may not be advisable for lithotresis to proceed at the fastest possible speed if over-riding reasons for a slower rate exist. In our later cadaver experiments, we found that a slow water drip, at approximately the rate of diuretic urine flow, through a flexible cannula inserted into the ureter above the stone aided greatly in drilling. Such a flow would correspond to the case of the nonobstructing stone.

We have tried injecting water through a small lumen plastic tube built into the wall of the catheter and ending at its tip. This did not accomplish our purpose because, with suction in the main lumen, injected water immediately re-entered the catheter without feeding the drill tip. The extra tube also took up considerable space in the catheter and distorted its lumen slightly, so that the ribbons tended to bind. A finer tube in the wall of a catheter did not maintain its lumen after construction. No doubt a better two-lumen catheter can be made, should this approach prove advisable.

In our last 12 attempts to drill artificial plaster stones in cadavers with the no. 11 multi-holed, single-lumen catheter containing four 1/32″ x 0.010″ monel ribbons soldered into a 4 mm. monel tube (no. 10), and using suction, the results are summarized as follows: We have fragmented or drilled completely through a central portion of the stone in three cases (see Fig. 4); have drilled part way through the central zone (stopping because of extraneous factors, such as breakage of a ribbon which could not be replaced in a cadaver in contradistinction to the clinical situation, or faulty judgment of the progress) in four cases; and have grooved the periphery of the stone with final bypassing in five cases. One stone has been counted twice, since first it was drilled part way through centrally and then it was grooved in a second trial. Some of these cases did not use methods we later decided were necessary, such as a uniform cross section of drill-tip to foster self-cleaning and avoid impaction.

V. CRITIQUE OF ULTRASONIC LITHOTRESIS

Cadaver experiments do not answer all the questions posed by the method when considered for clinical trial. The most obvious question concerns ultrasound and its possible harmfulness. Another question pertains

to the use of suction in the ureter: is it dangerous? Finally, is lithotresis, itself, subject to complications? There are other related problems that should be considered; some have already been discussed.

A minor concern in the clinical application of our cadaver experiments is the fact that the retrograde mode of inserting our drill wire ensemble may have the experimental disadvantage of not subjecting it to the sharp curves it would have passed through in the clinical route starting at the urethra, where only one end of the catheter is free and is pushed on, an application of force which tends to increase curvature. Our ribbons have a high flexion capacity. Encircling a two-inch diameter cylinder leaves practically no set. X-ray photographs, already cited, of the effect of four of these ribbons in a no. 9 catheter on the contours of a living ureter also showed little residual curvature in the ribbons after they were withdrawn.

At the start of our work with low frequency ultrasound, we were fearful of it, attempting to use instruments to manipulate any ultrasonically vibrating object. Gradually, familiarity bred increasing confidence in its harmlessness so long as pain from burning was avoided. We have noted no damage in our fingers as a result of handling activated objects. The many reports on the destructive effects of ultrasound refer to high frequencies quite outside our range.[4, 14, 24] Aside from the differential effects on nerve cells,[40] the effects noted at these frequencies can be ascribed to heat production[4, 24, 6] and to cavitation,[17, 38] which produces hydrogen peroxide.[5] Except for heating, we doubt that the intensities of ultrasound we employ are harmful. To avoid heating effects, we pulse our ultrasound. The catheter helps to reduce heat formation and to insulate the ureter, thereby reducing peak temperature. Experiments on dog ureters with our ribbons in standard no. 6 X-ray catheters from which they extend slightly are under way to determine the effects of our pulsed ultrasound. So far, the pathologist* has not been able to distinguish the treated from the untreated ureter removed one hour and 21 hours after an hour's exposure to the ultrasonic energy. The high density and heterogenous structure of the X-ray-opaque, woven catheter make it an excellent sound insulator. Furthermore, the sound, being coaxial, is poorly propagated radially to the ureter along the length of the catheter. Only at the drill tip, where the ureter is exposed directly, is there good transmission to the tissues. A conclusion on this vital subject must await further experimentation.

While there have been many attempts to destroy neoplasms with ultrasound, we are unaware of consideration that it may be neoplastogenic. At

* We are very much indebted to Dr. Sidney B. Weinberg for his unstinting helpfulness.

high frequencies and intensities, mutations can be produced by ultrasound, which would certainly suggest this possibility. We consider neoplasia quite unlikely at our low frequencies, so close to audible levels and with a wavelength very different from that of cells and nuclei.

We do not expect ultrasound to promote crystallization of salts from their super-saturated state in the urine. The urine flowing around the ultrasonic-vibrating ribbon from the ureteral catheter in a dog was found to be quite clear, and human urine also remained clear when ultrasonorated. Actually, the amount of super-saturation of urine is so small that, even if precipitation of salts did occur, the precipitate would be trivial in quantity and so finely divided as to be easily flushed from the ureter.

More to the point is the possibility that the fragmentation of ureteral calculi may provide nuclei for new stone formation, since experimentally this can occur in rats.[15, 39] Such a possibility assumes that the fragments are not drilled to a small size, that they are not flushed out by the urologist, that they are not passed spontaneously (which seems unlikely since smaller stones are more readily passed), and that the urine post-operatively is not maintained at a hydrogen-ion concentration, volume, and salt content (and perhaps protective colloid concentration) least favorable to further stone formation. We believe that the possibility of lithotresis leading to multiple calculi large enough to be a serious problem needs clinical evaluation, since animal studies are unlikely to be of decisive importance. Should this possibility be significant* the use of chelating fluids with ultrasound may be an important means to offset it.

Harm to the attachments of the ureter due to the proposed instrument seems highly unlikely, as shown by the X-ray photograph of a no. 9 catheter with four ribbons, and because baskets and other stiffer devices have already been employed with success. Perforation because of the square-cut drill-tip and the difficulty of passing a large instrument have already been discussed.

Experiments on animals to determine the effect on the ureter of suction of about 380 mm.Hg are necessary to ensure that this application is clinically justified. Such a pressure should interrupt blood flow in the tissue which bears its brunt. It seems likely that suction should not be maintained for long periods without interruption. Suction should be no more disturbing than tourniquets applied elsewhere to the body.

In the lower third of the ureter, where calculosis is commonest, suction may not be necessary, except possibly for the brief period (two minutes or less) which may be needed if the drill tip otherwise tends to bypass the

* Browne[8] mentions occasional crumbling of a stone by a catheter bypassing it without noting any untoward consequences.

stone and this result is not desired. Higher in the ureter, it may well be that suction, should it be harmful, may not be needed except to set the drill in the stone. After this has been accomplished, angulation may be unimportant or may be reduced sufficiently by traction on the catheter below the slipping point so that the hollow drill can be pressed mechanically into a stone it has already started to penetrate.

Furthermore, lithotresis need not employ suction at all so long as a catheter bypasses a stone. The ureter will thus be effectively splinted and an ultrasonic drill can then be passed alongside the catheter. Even with angulation, repeated bypassing with grooving should be effective lithotresis. If bypassing alone without lithotresis is all that is accomplished by ultrasound, obstruction is relieved and the classical methods for manipulative removal of the stone remain. We believe that bypassing of the stone by the drill should be possible almost as often as desired.

The whole matter of skewing of the drill and bypassing the stone arose in models of the ureter and in the cadaver. Its actual importance in man is not known. In an X-ray, our four ribbons in a no. 9 catheter caused little ureteral angulation in a patient without a stone. Traction on the ureter below the stone greatly diminishes the likelihood of skewing in the cadaver. Traction may be applied by the natural friction between ureter and the large drill-catheter, or, if inadequate in man* suction will certainly provide sufficient transmission of traction, provided it is harmless and does not cause interposition of ureter wall between drill and stone. Finally, it may well be that pressure and manipulation by the urologist's hand on the wall of the anesthetized abdomen, alone or with traction, without suction, may suffice to prevent angulation between stone and drill long enough for the desired seating of drill on stone to be accomplished. Should suction be harmless and initially desirable to prevent slippage of the catheter with resulting skewing of the drill, the occasionally untoward interposition of ureter wall between drill and stone caused by the high 380 mm.Hg vacuum may be avoided without loss of the benefits of suction. The vacuum might be reduced so that the drill can push aside any interposing ureter wall, or suction might be limited to the four-inch portion of the catheter before the drill tip where the holes are now placed (Fig. 2). This could be accomplished by means of a second small lumen in the catheter wall with special means for distributing the suction effectively. Such a method would have the virtue of permitting ureteral traction with suction all the time, while the main lumen was

* The traction to move a no. 9 catheter in the case cited was between 30 and 50 grams; a no. 11 catheter may not offer sufficient friction, if angulation is a clinical problem.

freely used independently for water, alternating with suction if desired—drill force being supplied externally as required.

Our cadaver experiments were based on having a supply of water at the drill, as when the stone produces only a partial obstruction.

Where urine flow is inadequate or absent (of course the kidney is presumed functional), an initial charge of water into the catheter may permit the drill to start and, in such a case, a procedure to promote bypassing of the stone rather than lithotresis would seem in order, since relief of renal obstruction would be the first objective. This may be accomplished, our experience would suggest, by using no suction, only as much traction on the catheter at the urethra* as is needed to reduce angulation to perhaps 30° from the straight line, and moderate drilling force (about 80 grams) at the cone. Should subsequent clinical experience demonstrate that such a method is not valuable, either water can be supplied by methods to be discussed or bypassing can be better promoted by a smaller solid drill tip which deflects readily. To avoid perforation, the drilling force would be carefully restricted.

If an external water source rather than urine from the kidney should prove necessary clinically, it may be supplied by injection through the catheter periodically, as drilling and suction are suspended. This may have the disadvantage of tending to unseat the drill on the stone. However, once the drill is started, this seems unlikely, unless fresh urinary calculi in the ureter fragment much more easily than plaster-of-Paris. In that event, the speed of lithotresis would be very great, and reseating the drill may not need to be accomplished more than once or twice.

Ideally, we should like a controllable means of applying water at the drill tip, Possibly a tiny tube attached to the drill can accomplish this, either being very flexibly connected to a second lumen in the catheter or continuing along with the ribbons within the bore of the catheter.

Possibly fluids other than water and chelating fluids, and perhaps suspensions of harmless abrasives, may aid lithotresis clinically.

The mulberry type of stone or any other with sharp spicules should not be removed by classical manipulation, since it may easily damage the ureter because of its sharpness, large size, and the force needed to move it. Possibly lithotresis may break such a stone into fragments small enough so that they are not a danger when passed through the urinary tract. On the other hand, the reverse may be true: many small spicules may multiply this hazard. Here, too, clinical evaluation seems essential.

---

* Such traction, if applied to the catheter at the urethra, with the catheter then curved towards the cone, does not supply drilling force.

Should the methods outlined prove clinically adaptable, they would have the advantage of extending upward in the ureter the zone in which manipulative removal of urinary calculi is preferred to operation. The size of stone which might be attacked manipulatively may also be radically increased by ultrasonic lithotresis.

ACKNOWLEDGMENT

We wish to record here our heartfelt gratitude to Dr. Jane Northup for her effective, indefatigable, and friendly help and encouragement.

REFERENCES

1 Abeshouse, B. S. and Weinberg, T.: Action of versene on urinary calculi. *J. Urol.*, 1951, *65*, 316.

2 Albright, F., Sulkowitch, H. W., and Chute, R.: Nonsurgical aspects of the kidney stone problem. *J. Am. M. Ass.*, 1939, *113*, 2049.

3 Am. Soc. Metals, Metals Handbook Committee: *Metals handbook*. Cleveland, Ohio, 1948.

4 Bender, L. F., Herrick, J. F., and Krusen, F. H.: Temperatures produced in bone by various methods used in ultrasonic therapy. *Arch. Phys. M. Rehab.*, 1953, *34*, 424.

5 Bergmann, L.: Ultrasonic damage. *Der Ultraschall*. Zürich, S. Hirzel, 1949, p. 627.

6 Bickford, R. H. and Duff, R. S.: Influence of ultrasonic irradiation on temperature and blood flow in human skeletal muscle. *Circ. Res.*, 1953, *1*, 534.

7 Blackrie, A.: *A disquisition on medicine that dissolves the stone. In which Dr. Chittick's secret is considered and discovered.* London, 1766.

8 Browne, H. S.: Experiences with ureteral calculi. *J. Urol.*, 1943, *50*, 301.

9 Butt, A. J.: Rôle of protective urinary colloids in prevention of renal lithotresis. *Tr. Am. Urol. Ass.* (Southeast. Sect.), 1951, March, 1.

10 Butt, A. J. and Hauser, E. A.: The importance of protective urinary colloids in prevention and treatment of kidney stones. *Science*, 1952, *115*, 308.

11 Champion, W. L., Fowler, M. F., Coleman, R. C., Jr., and Florence, T. J.: Management of calculi in lower ureter. *Tr. Am. Urol. Ass.* (Southeast. Sect.), 1951, March, 11.

12 Dourmashkin, R. L.: Cystoscopic treatment of stones in the ureter with special reference to large calculi; based on the study of 1550 cases. *J. Urol.*, 1945, *54*, 245.

13 Ellik, M.: Stones in the ureter: Their extraction by looped catheter. *J. Urol.*, 1947, *57*, 473.

14 Fry, W. J., Mosberg, W. H., Jr., Barnard, J. W., and Fry, F. J.: Production of focal destructive lesions in the central nervous system. *J. Neurosurg.*, 1954, *11*, 471.

15 Grove, W. J., Vermeulen, C. W., Goetz, R., and Rogins, H. D.: Experimental urolithiasis. II. The influence of urine volume upon calculi experimentally produced upon foreign bodies. *J. Urol.*, 1950, *64*, 549.

16 Hales, S.: *An account of some experiments and observations on Mrs. Stephen's medicines for dissolving the stone . . .* London, T. Woodward, 1740.

17 Harvey, E. N.: Biological aspects of ultrasonic waves, a general survey. *Biol. Bull.*, 1930, *59*, 306.

18 Keyes, E. L.: The Joanna Stephens medicines for the stone, a faith that failed. *Bull. N. York Acad. M.*, 1942, 2d ser., *18*, 835.

19 Kittredge, W. E. and James DeW.: Management of ureteral calculi. *Tr. Am. Urol. Ass.* (Southeast. Sect.), 1953, March, 24.

20 LeDuc, E.: Management of patients with ureteral stone. *Urol. Surv.*, 1953, *3*, 303. (Abstract from *California M.*, 1953, *78*, 127.)

21 Lamport, H.: Ultrasonic probe to drill. Application for grant to the Dazian Foundation, May 15, 1950.

22 Lamport, H., Newman, H. F., and Eichhorn, R. D.: Fragmentation of biliary calculi by ultrasound. *Fed. Proc., Balt.*, 1950, *9*, 73.

23 Lucas, O. C., Stevenson, J. S., and Stevenson, L. S.: Petrologic study of a urinary calculus. *Tr. R. Soc. Canada*, 1950, *44*, 35.

24 Lynn, J. G., Zwemer, R. L., Chick, A. J., and Miller, A. E.: A new method for the generation and use of focussed ultrasound in experimental biology. *J. Gen. Physiol.*, 1942, *26*, 179.

25 MacAlpine, J. B.: *Cystoscopy and urography*, 3d. ed. Bristol, John Wright and Sons, Ltd., 1949. p. 338.

26 Mason, W. P.: *Piezo-electric crystals and their application to ultrasound.* New York, D. Van Nostrand, 1950. p. 412.

27 Mason, W. P. and Wick, R. F.: A barium titanate transducer capable of large motion at an ultrasonic frequency. *J. Acoust. Soc. Am.*, 1951, *23*, 209.

28 McCarthy, J. F.: Upper urinary tract calculus. *J. Urol.*, 1950, *64*, 295.

29 Nesbit, R. M., moderator. Panel discussion on urolithiasis. *Urol. Surv.*, 1954, *4*, 2.
a. Priestley, J. T.
b. Ellik, M.
c. Suby, H. L.
d. Prien, E. L.

30 Neuberg, C. and Mandl, I.: An unknown effect of amino acids. *Arch. Biochem.*, 1948, *19*, 149.

31 Neuberg, C. and Mandl, I.: Beachtliche Wirkung von Salzen organischer Säuren auf unlösliche anorganische Verbindungen (Mineralysis). *Zschr. Vitaminforsch., Bern*, 1949, *2*, 480.

32 Oman, C. R. and Applebaum, E.: Ultrasonic cavity preparation. Preliminary report. *N. York State Dent. J.*, 1954, *20*, 256.

33 Prentiss, R. J., Mullenix, R. B., and Whisenand, J. M.: The management of ureteral stone. *Urol. Surv.*, 1952, *3*, 30.

34 Prien, E. L.: Studies in urolithiasis: II. Relationships between pathogenesis, structure, and composition of calculi. *J. Urol.*, 1950, *61*, 821.

35 Prien, E. L. and Frondel, C.: Studies in urolithiasis: I. The composition of urinary calculi. *J. Urol.*, 1947, *57*, 949.

36 Smith, F. D.: The destructive effect of bubbles liberated by cavitation. *Philos. Mag.*, 1935, *19*, 1147.

37 Suby, H. I., Suby, R. M., and Albright, F.: Properties of organic acid solutions which determine their irritability to the bladder mucuous membrane and the effect of magnesium in overcoming this irritability. *J. Urol.*, 1942, *48*, 549.

38 Trevis, P., Henricks, J. R., and Archer, W. A.: *Contributions towards a flora of Nevada*, No. 33, Part II. U.S. Dept. Agri., 1941.

39 Vermeulen, C. W., Grove, W. J., Goetz, R., Rogins, H. D., and Correll, N. O.: Experimental urolithiasis. I. Development of calculi upon foreign bodies surgically introduced into bladders of rats. *J. Urol.*, 1950, *64*, 541.

40 Wulff, V. J., Tucker, D., Fry, F. J., and Melton, C.: Effects of ultrasonic vibrations on nerve tissue. *Proc. Soc. Exp. Biol., N.Y.*, 1951, *76*, 361.

HERMANN J. SCHAEFER*
ABNER GOLDEN†

U. S. Naval School of Aviation Medicine, U. S. Naval Air Station, Pensacola, Florida, and the Department of Pathology, Emory University School of Medicine, Emory University, Georgia

THE EFFECTIVENESS OF COLLOIDAL THORIUM DIOXIDE AS AN INTERNAL ALPHA EMITTER: A COMBINED MORPHOLOGIC AND RADIOAUTOGRAPHIC STUDY‡

The hazard of ionizing radiation from internally administered colloidal thorium dioxide (Thorotrast) has been a subject of controversy even since this medium was first employed in clinical roentgenology. Reports of neoplasia as well as diffuse hepatic fibrosis occurring in patients following Thorotrast administration have been summarized and evaluated by Thomas *et al.*[7] Although intravenous injection of colloidal thorium dioxide introduces a highly potent source of intense alpha radiation into certain tissues of the body, a combined histologic and radioautographic study clearly indicates that the tissues are exposed to but a fraction of the total ionization dosage and that most of the radiation energy is dissipated within the thorium deposits themselves.

METHODS

Groups of rabbits were given Thorotrast intravenously in doses of 9, 18, and 27 cc. and were sacrificed after 24 hours, 1, 4, and 9 months.

Hematologic studies were performed at frequent intervals during the experiment and included blood hemoglobin concentration, red blood cell, reticulocyte, white blood cell, and differential counts. The animals were sacrificed by nembutal anesthesia. Tissues were fixed in absolute alcohol, 10 per cent Formalin, U.S.P. and Zenker's fluid with 5 per cent acetic acid. Histologic sections were stained routinely with hematoxylin and phloxine and with Mallory's aniline blue and in certain instances by the periodic acid-Shiff and Feulgen methods. Representative sections of all major organs were studied although emphasis was placed on liver, spleen, and bone marrow.

The method of radioautography employed in this study has been described in detail elsewhere.[6] The fully processed histologic preparation is brought into direct contact with a nuclear emulsion plate. Following the radioautographic exposure (68 to 72 hours), the combined preparation is exposed briefly to a source of visible light so that

---

* Biophysicist, U. S. Naval School of Education, Pensacola.

† Associate Professor of Pathology, Emory University School of Medicine.

‡ This study was aided by a contract between the Office of Naval Research, Department of the Navy, and Emory University, NR 119-181.

Received for Publication May 12, 1955.

the pattern of various clear spaces in the histologic preparation is printed on the photographic emulsion. This pattern is utilized for subsequent alignment of tissue section and radioautograph. The method permits accurate localization of alpha radiating deposits and careful histologic search for radiation damage to nearby cells.

OBSERVATIONS

All rabbits gained weight and appeared healthy throughout the experimental period.

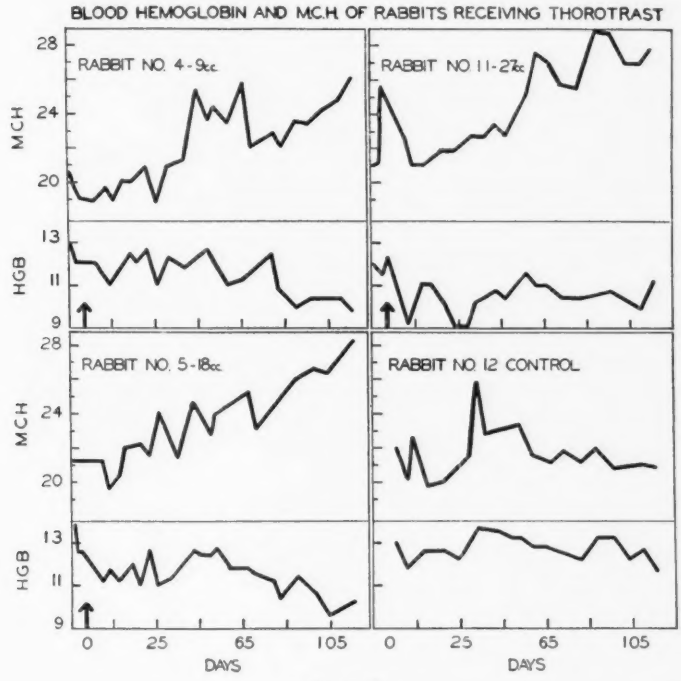


CHART 1.

The significant hematologic observations in the rabbits maintained for four and nine months following injection are summarized in Charts 1 and 2. All rabbits showed a distinct tendency toward a macrocytic anemia. The blood hemoglobin concentration diminished only slightly but there was a marked drop in total red blood cell count. No significant changes were noted in reticulocyte counts or in leukocyte and differential counts.

Histologic studies showed rapid phagocytosis of Thorotrast by cells of the reticuloendothelial system, particularly in liver, spleen, and bone marrow. Phagocytosis appeared to be virtually complete after 24 hours. Deposits were also present to a lesser degree in organs such as adrenals, lungs, kidneys, gastrointestinal tract, and lymph nodes. Only rare instances of extracellular tissue deposition were encountered and these deposits were minute in size. When studied with the Mallory aniline blue method, the

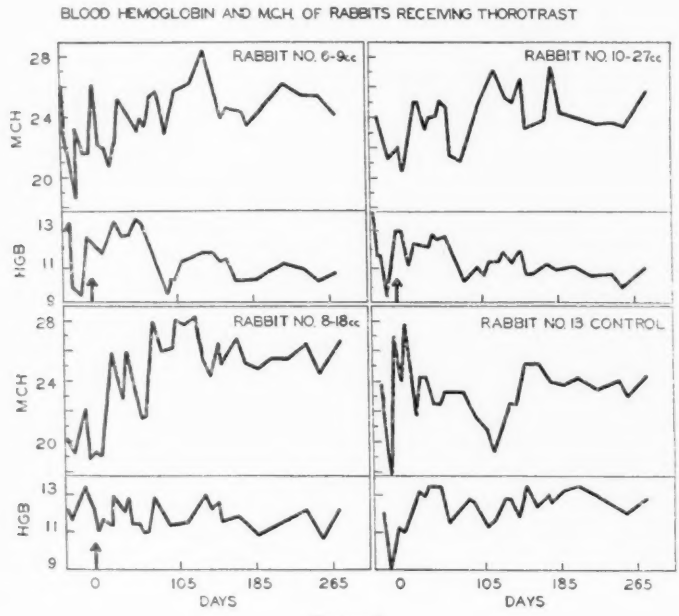


CHART 2.

deposits took a faint bluish stain in the tissues of the rabbit sacrificed 24 hours after injection but stained deep blue in animals maintained for one month or longer.

The most striking morphologic observation was the accumulation of Thorotrast in progressively larger masses during the period of the experiment. This progressive enlargement appeared to be due first to enlargement of individual reticuloendothelial cells followed later by the formation of large reticuloendothelial giant cells. This change in the size of the reticuloendothelial deposits is illustrated in Figures 1, 2, and 3. Although evident

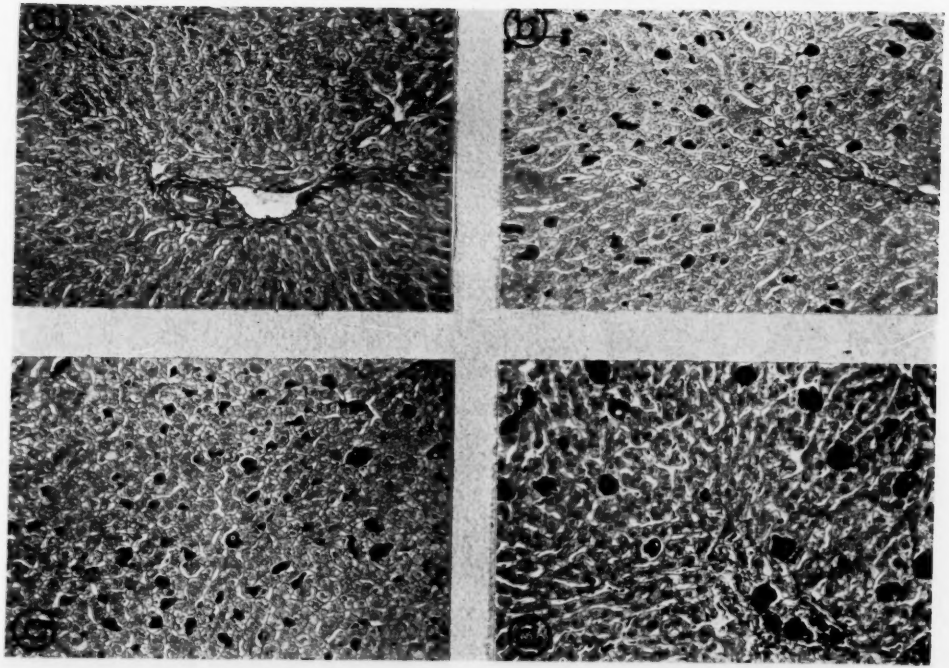


FIG. 1. Histologic sections of liver from rabbits sacrificed 24 hours (a), 1 month (b), 4 months (c), and 9 months (d) following intravenous Thorotrast injections. The Thorotrast deposits appear as black masses in the photomicrographs. A few tiny deposits are visible after 24 hours, but progressively larger masses are seen as the experimental period is extended. Aniline blue x80.

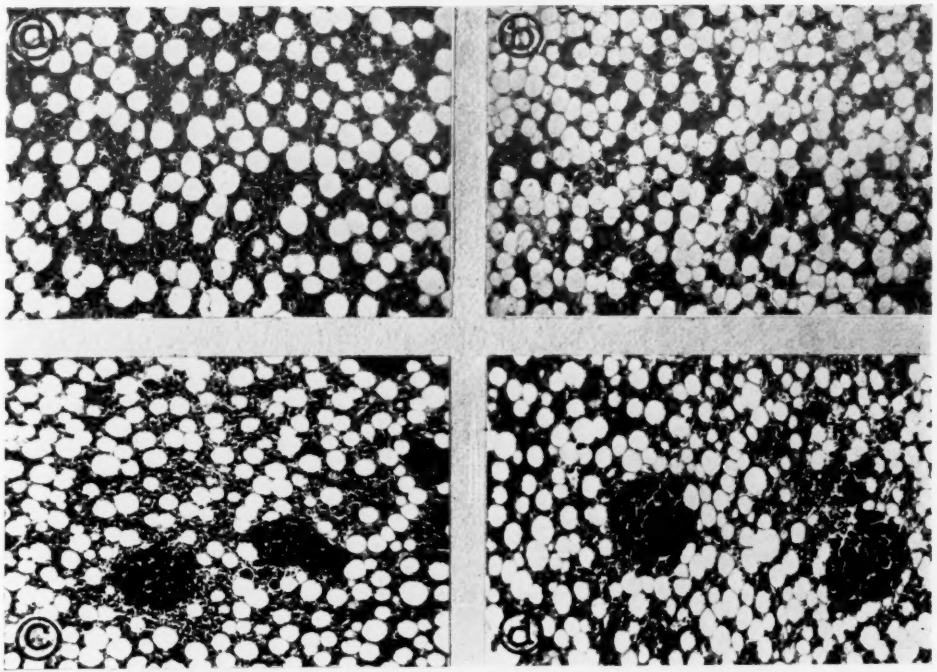


FIG. 2. Histologic sections of bone marrow from rabbits sacrificed 24 hours (a), 1 month (b), 4 months (c), and 9 months (d) following intravenous Thorotrast injections. Progressive enlargement of the Thorotrast deposits is again apparent. Aniline blue x80.

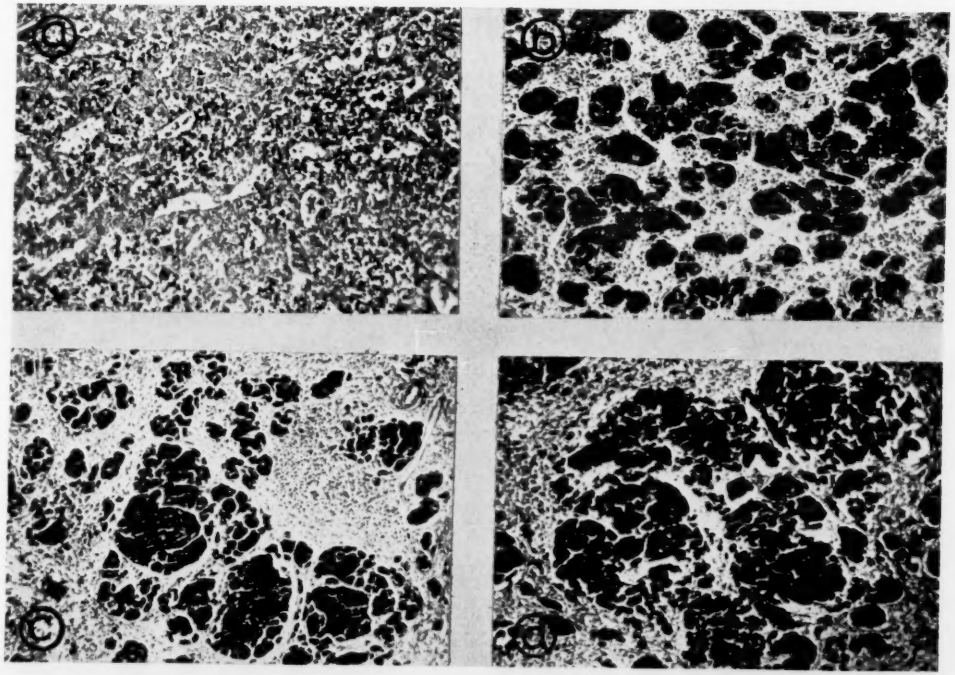


FIG. 3. Histologic sections of spleen from rabbits sacrificed 24 hours (a), 1 month (b), 4 months (c), and 9 months (d) following intravenous Thorotrast injections. Progressively larger Thorotrast deposits are seen with formation of conglomerate masses after 4 and 9 months. Aniline blue x80.

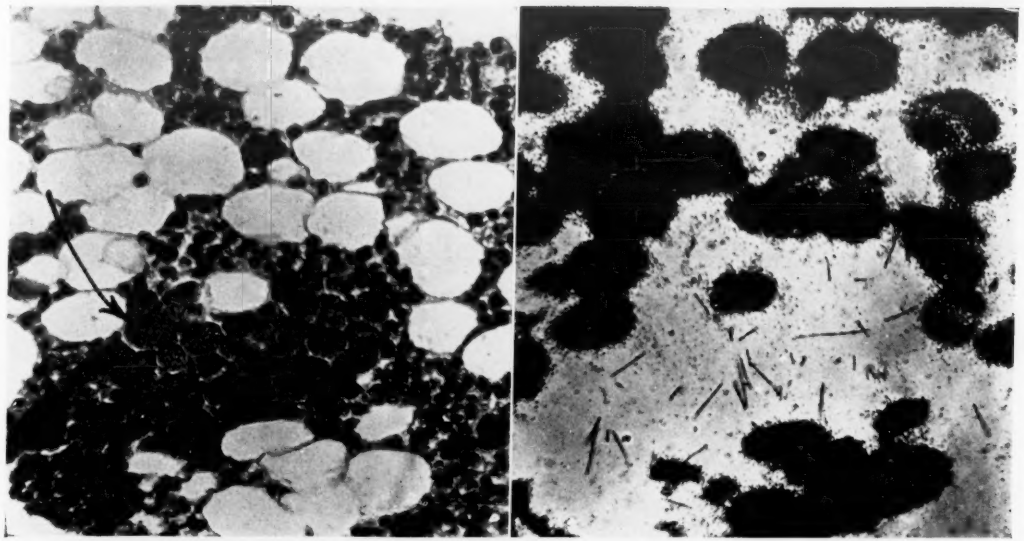


FIG. 4. *Left.* Tissue section of bone marrow. Hematoxylin and phloxine x330. *Right.* Radioautograph x330. The dark masses in the radioautograph correspond to the clear fat cells in the histologic preparation. The alpha tracks seen in the radioautograph can be localized in a large group of Thorotrast-laden cells (arrow). It is apparent that most of the alpha particles dissipate their energy within the thorium deposits and that only a few reach nearby hematopoietic cells.

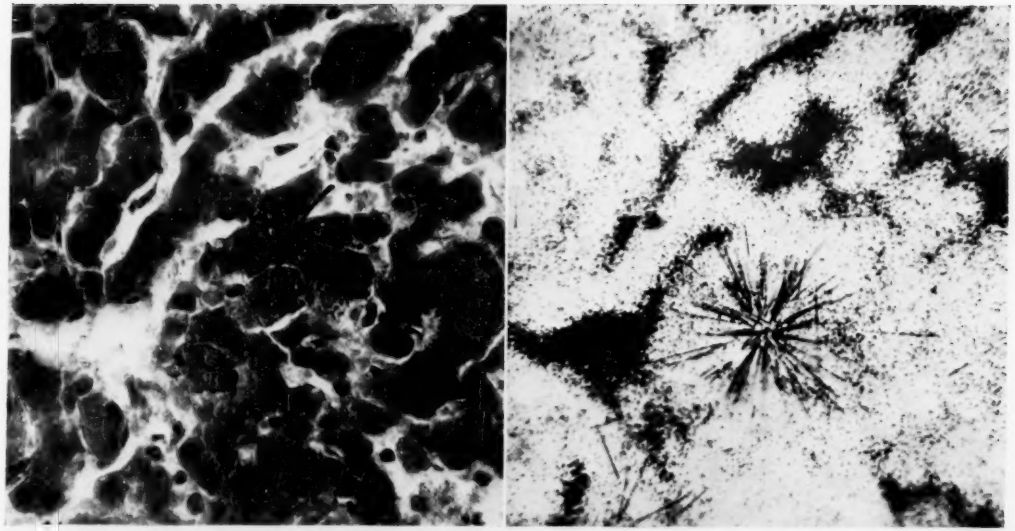


FIG. 5. *Left.* Tissue section of liver. Hematoxylin and phloxine x370. *Right.* Radioautograph x370. The dark granular areas in the radioautograph correspond to the hepatic sinusoids. The intense source of alpha radiation seen in the autograph can be localized in a Thorotrast-laden Kupffer cell (arrow). The surrounding liver cells show no morphologic evidence of injury, suggesting that the peak ionization dosage from this source is being dissipated in the Thorotrast deposit itself.

in liver, the change was more prominent in the bone marrow and the spleen. In the latter, tremendous conglomerate deposits formed.

The large deposits of Thorotrast appeared to be quite bland. Occasional disintegration of reticuloendothelial cells was noted, particularly in the liver. This degeneration was associated with slight lymphocytic infiltration but appeared to heal without scarring.

The organs examined at the end of nine months showed few changes other than the large deposits of thorium dioxide. The bone marrow appeared normally cellular. The architectural pattern of the liver was well maintained and there was no evidence of significant fibrosis. The tremendous deposits in the spleen made evaluation of fibrosis difficult but this appeared to be at most minimal. With a single exception (*vide infra*) there were no abnormal findings in other organs that contained less thorium. No instances of neoplasia were encountered in any of the material studied.

Radioautographs permitted localization of the most active deposits of thorium and careful study of nearby cells for evidence of radiation injury. Figure 4 shows a section of bone marrow together with its radioautograph. The alpha tracks seen in the autograph can be localized in the group of Thorotrast-laden cells in the lower portion of the photomicrograph. It is apparent that the energy of the alpha particles is being released largely within the thorium deposits and that little, if any, is reaching the surrounding hematopoietic tissue. Figure 5 shows a section of liver and its radioautograph. A source of intense alpha radiation, a "star center," is seen in the radioautograph and can be localized in a Kupffer cell of the liver. Most of the emanations of thorium appear as scattered single tracks. Foci of intense activity such as shown here are an only occasional finding but provide an unusual opportunity to search for cellular injury. The liver cells surrounding the active deposit in Figure 5 show no evidence of injury. All similar star centers encountered were subjected to detailed histologic study. In the vast majority of instances, the radioautographic studies suggested that the peak of ionization dosage was dissipated in the large thorium masses themselves and that only a small proportion of the total dosage reached the surrounding cells. In only one instance, to be reported,[2] did we observe injury to a single intestinal mucosal cell adjacent to a star center of alpha radiation. It is significant that this solitary example of cell damage was in relation to a minute extracellular thorium deposit rather than one of the large reticuloendothelial deposits.

The alpha activity in the various organs was determined from track counts of the radioautographs. Chart 3 shows the alpha dosage rates ex-

pressed in roentgens equivalent physical per day for spleen, bone marrow, and liver. Chart 4 shows the total dosage released in these organs during the indicated experimental periods.

DISCUSSION

Thorium is primarily an alpha emitter. The thorium disintegration series includes six alpha emitters and four beta emitters, but the total energy of the alpha emitters is more than 10 times that of beta emitters.[5] The specific ionization, i.e., the energy dissipation per unit path length, is much higher

CHART 3. ALPHA DOSAGE RATE EXPRESSED IN R. E. P. PER DAY

Thorotrast dose		*Time after injection*			
cc.	*Organ*	*1 day*	*1 month*	*4 months*	*9 months*
9	Spleen	5.3	4.9	2.6	3.6
9	Marrow	0.67	0.55	0.41	0.70
9	Liver	0.54	...	0.23	0.43
18	Spleen		4.0	3.1	10.1
18	Marrow		1.1	0.51	0.60
18	Liver		1.8	0.60	0.43
27	Spleen		7.7	8.7	9.0
27	Marrow		1.6	2.3	2.3
27	Liver		1.2	0.67	1.3

for alpha than beta particles, resulting in a greater effectiveness of alpha radiation per dissipated unit of energy. The beta rays, due to their longer range, spread their energy over a much larger tissue volume. It is apparent that the radiation effect from incorporated thorium and its decay products centers almost exclusively in the alpha component. A single intravenous injection of Thorotrast (colloidal thorium dioxide) introduces into the body a significant quantity of alpha active matter.* An injection of 50 cc. to a human subject incorporates an activity of 3.6 microcurie. This is 36 times the maximum permissible amount of radium fixed in the body as defined in the International Recommendations.[3]

* Thorotrast is stated to contain 24 to 26 per cent thorium dioxide by volume. Since the density of thorium dioxide is 9.7, the density of the solution should be about 3.0. We have carefully checked the density of Thorotrast and find it to be 1.31, indicating a concentration of thorium dioxide of only 3.6 per cent. This figure has been checked by measuring the alpha radiation from thin films of the solution by track count in nuclear emulsion. The activity was found to be 7.3×10^{-2} microcurie per cc. of Thorotrast. This figure is probably 20 per cent low because we did not achieve full 4π geometry.

Our morphologic observations indicate that the deposits of thorium dioxide are in virtually all instances quite bland. Thorium accumulated in progressively larger deposits during the nine months' experimental period. Although the reticuloendothelial cells containing the deposits occasionally appeared to degenerate, this was associated with only slight inflammation and repair occurred without fibrosis. Nine months after injection, the organs revealed no architectural derangement or significant fibrosis, and no instances of neoplasia or cellular atypism were seen. Although distinct tumors have been produced experimentally in animals by injection of

CHART 4. TOTAL ALPHA DOSAGE IN R. E. P. FROM INJECTION TO TIME OF SACRIFICE

Thorotrast dose		*Time after injection*			
cc.	*Organ*	*1 day*	*1 month*	*4 months*	*9 months*
9	Spleen	5.3	147	307	1086
9	Marrow	0.67	16	50	209
9	Liver	0.54	...	28	128
18	Spleen		119	368	3024
18	Marrow		32	61	180
18	Liver		53	71	128
27	Spleen		230	1045	2700
27	Marrow		48	270	702
27	Liver		35	81	396

Thorotrast,[1] it is of interest that this has been accomplished only with extravascular injection where a highly effective tissue dosage of alpha radiation can be applied at a local site. We found only a single isolated example of cell injury related to thorium deposition, and in this instance, the deposit was minute in size and extracellular in location.[2]

It is apparent that there is a major inconsistency between the total dosage of alpha radiation shown in Chart 4 and the lack of morphologic evidence of radiation injury that would be expected with the application of such heavy dosage to the body cells. The key to this discrepancy lies in the size of the thorium deposits. The large deposits limit the effectiveness of alpha radiation, and their progressive enlargement during the nine-month period results in a progressive decrease in effective radiation.

The tissue ranges of alpha particles emitted by the thorium series vary between 35 and 113 micra. By virtue of its density, thorium itself would have a "stopping" effect greater than that of tissue. If we assume that the intracellular deposits consist of thorium dioxide plus protective colloid, we

obtain a specific gravity for these deposits of 2.25. This would mean that the range of the alpha particles in the deposits proper would be 76 per cent of that in tissue. Preliminary electron microscope observations of Thorotrast deposits, however, suggest that thorium may comprise one-half of the deposits. If this is the case, the range of the alpha particles within the deposits would be considerably less.

The size of the Thorotrast deposits indicates that a large part of the total alpha energy is dissipated in the material of the deposits and is conse-

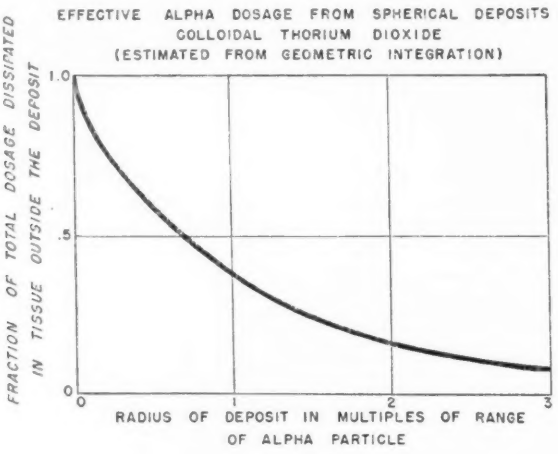


CHART 5.

quently lost for actual tissue dosage. If one assumes a spherical shape for the deposits and takes into consideration the ranges of the various alpha particles, one can calculate by geometric integration the fraction of the alpha dosage that is administered to the surrounding tissue. Chart 5 shows the results of this calculation. It is obvious that for a deposit of diameter zero (molecular dispersion of active substance) the full dosage is dissipated in tissue. For an infinitely larger deposit, the effective dosage contribution from the thin surface layer is negligible when compared to total dosage so that the curve must approach zero utilization. For convenience, the radius of the deposits is plotted in multiples of the range of the alpha particles.

The deposits of thorium in the Kupffer cells of the liver are roughly spherical. From the size of the deposits, we have estimated that 70 per cent of the total dosage of alpha activity in the liver is effective as tissue dosage. In bone marrow, the mean radius of the deposits indicates as little as 24

per cent effective component of the total dosage administered. The deposits in the spleen are nonspherical and highly irregular, but we have estimated effective tissue dosages of 15, 8, and 5 per cent for the rabbits sacrificed nine months after receiving 9, 18, and 27 cc. of Thorotrast.

Chart 6 shows the effective tissue dosages in roentgens equivalent physical applied during the experimental periods. These figures were determined by applying the principles outlined above to the total dosages shown in Chart 4. The effective tissue dosages are still of considerable magnitude and

CHART 6. CALCULATED TOTAL EFFECTIVE TISSUE DOSAGE (ALPHA) IN R. E. P. FROM INJECTION TO TIME OF SACRIFICE

Thorotrast dose		*Time after injection*			
cc.	*Organ*	*1 day*	*1 month*	*4 months*	*9 months*
9	Spleen	.80	22	46	163
9	Marrow	.37	8.8	28	115
9	Liver	.38	...	20	90
18	Spleen		9.5	29	242
18	Marrow		11	21	61
18	Liver		37	50	90
27	Spleen		12	52	135
27	Marrow		10	54	140
27	Liver		25	57	278

suggest that a more prolonged experiment might reveal morphologic evidence of significant radiation injury.

The macrocytic anemia shown by all of the rabbits maintained four or nine months after injection is difficult to interpret. Similar changes in hematologic pattern have been described previously. Reeves and Stuck[4] gave doses of Thorotrast of 40 cc. per kilo to rabbits and observed an erythroblastic anemia without reticulocytosis. They considered this anemia consistent with changes related to the presence of a colloidal substance in the bone marrow rather than due to its radioactivity.

SUMMARY

Colloidal thorium dioxide (Thorotrast), administered intravenously to rabbits, accumulated in progressively larger deposits in reticuloendothelial cells, principally in the liver, spleen, and bone marrow. These deposits appeared to be quite bland and no evidence of hepatic fibrosis or instances of neoplasia were observed nine months after injection. Radioautographic

studies indicated that a significant proportion of the energy of alpha radiation released during the experimental period was dissipated within the thorium deposits themselves and was ineffective for tissue dosage.

REFERENCES

1 Foulds, L.: The production of transplantable carcinoma and sarcoma in guinea-pigs by injections of Thorotrast. Am. J. Cancer, 1939, *35*, 363.
2 Golden, A. and Schaefer, H. J.: Injury to a single cell produced by microfocal alpha irradiation. (Unpublished.)
3 Recommendations of the International Commission on Radiological Protection. National Bureau of Standards, Handbook 47. Washington, 1950.
4 Reeves, D. L. and Stuck, R. M.: Clinical and experimental results with Thorotrast. Medicine, 1938, *17*, 37.
5 Rutherford, E., Chadwick, J., and Ellis, C. D.: *Radiations from radioactive substances.* Cambridge, Cambridge University Press, 1951.
6 Schaefer, H. J. and Golden, A.: Micro-alignment of alpha radioautographs by means of a contact replica of the tissue pattern printed with visible light. Exp. Cell Res., 1953, *5*, 545.
7 Thomas, S. F., Henry, G. W., and Kaplan, H. S.: Hepatolienography: past, present, and future. Radiology, 1951, *57*, 669.

FRANK L. GRUSKAY*
LEONELL C. STRONG†

Department of Anatomy, Yale University

CORRELATION BETWEEN MENDELIAN RECESSIVE TRAITS AND THE RESISTANCE TO FIBROSARCOMA IN MICE‡

INTRODUCTION

The influence of heredity on the induction of tumors in experimental animals has received wide attention from investigators in many laboratories. Information has accumulated in the past forty years which warrants a conclusion that a predisposition to cancer, or a sensitivity of the tissues to cancer, is inherited in some fashion. Reinhard and Candee,[18] as well as Strong,[29] Andervont,[3] Boyland and Warren,[4] and others, have shown that strains of mice vary in their susceptibility to carcinogen-induced tumors.

If the human organism is found to react to disease in exactly the same way as do certain animals, such as mice, we would be justified in holding the same conceptions concerning the nature of neoplasms as are held by the many geneticists working in the field of cancer in experimental animals. But we are inclined to believe that in regard to human beings statistics so far do not support such conclusions and it remains one of those matters which time and proper study of cases and their classification must eventually clarify.

Andervont,[3] Strong,[28] and others have found an intermediate susceptibility of the F_1 generation to carcinogenic agents when compared with the parent strains. This investigation was designed to determine the susceptibility of the F_1 generation and that of the backcross to the recessive parent, and to correlate these facts with older data from other investigations.

MATERIAL AND METHODS

Two pedigreed strains of mice provided by one of the authors have been used in this investigation, the pBr and the I strains, in addition to several hybrid generations resulting from the crossbreeding and the backcross of mice of these two original

---

* Intern, Pediatric Service, Grace-New Haven Community Hospital, 1954-55.
† Formerly Research Associate in Anatomy, Yale University School of Medicine. Present address: Roswell Park Memorial Institute, Springville, New York.
‡ This work was assisted, in part, by a grant from the James Hudson Brown Memorial Fund of the Yale University School of Medicine and grants to Dr. Strong from the Anna Fuller Fund. It was presented to the Yale University School of Medicine (by Gruskay) in partial fulfillment of the requirements for the M.D. degree.
Received for publication April 1, 1955.

strains. The origin of the pBr and I strains will be discussed only briefly here. Strong separated the pBr line from the original NHO strain in the F_{13} generation of brother-sister matings. The NHO line was originated by crosses of mice of the CBA, the JK, and the N ancestral stocks. pBr mice have the genes for pink eye, brown coat, and non-agouti. This line is now in the F_{44} generation of sib mating. The I strain originated in the laboratory of Dr. W. E. Castle at Bussey Institute, Harvard University. At that time the mice were not inbred, but have continued in sib matings by Strong for fifty-five generations.

Tables 1, 2, and 3 describe the mice used in these studies as well as their genetic constitutions and relationships. The total number of mice used in the investigation was 1,621, including animals used for breeding of the new hybrid mice. Inspection of

TABLE 1. SYNTHESIS OF THE MOUSE GROUPS USED IN THE INVESTIGATION

Parental strain	*Offspring designation*
pBr male x I female	F_{1a}
I male x pBr female	F_{1b}
F_{1b} male x I female	F_{2a}, F_{2b}, F_{2c}, F_{2d}
I male x F_{1b} female	F_{2f}, F_{2e}, F_{2g}, F_{2h}

TABLE 2. GENETIC CONSTITUTION OF THE MOUSE GROUPS USED IN THE INVESTIGATION

Strain	*Genotypes*
pBr	*aappbbSSDD*
I	*aappbbssdd*
F_1	*aappbbSsDd*
F_{2a}, F_{2e}	*aappbbSsDd*
F_{2b}, F_{2f}	*aappbbSsdd*
F_{2c}, F_{2g}	*aappbbssDd*
F_{2d}, F_{2h}	*aappbbssdd*

Tables 1 and 2 shows that the only difference amongst the several strains studied is the dominance or recessiveness of the genes at the *S-s* and *D-d* loci.

Concerning the use of mice of inbred strains, Strong[33] reports that biological variability within a particular strain has been reduced to a minimum. This fact has been shown over and over again, and for this reason biological research can be placed on a quantitative basis.

One milligram of methylcholanthrene dissolved in 0.1 cc. of sesame oil was injected subcutaneously into the right scapular region of the animal at 60 days of life. The oil has previously been tested and found to be noncarcinogenic by Andervont[2] and others.[6] Gardener,[7] however, reported four cases of sarcoma arising from the use of sesame oil itself, but these results have not been verified by any other investigator. Several other media for methylcholanthrene have been tried by others[2] with no resulting influence on the carcinogenicity of the compound. The animals were then examined weekly for evidence of tumor growth by the same observer throughout the investigation, and the time at which the tumor first appeared was recorded. The latent period was taken to be the time interval expressed in days between injection of the carcinogenic agent and the palpation of a definite tumor. All mice dying or killed during the experiment were examined at autopsy and all lesions were fixed in Bouin's fixitive and stained with hematoxylin and eosin.

The experiment was continued until all mice had either died or developed tumors. Those mice dying before the appearance of the earliest tumors were excluded from the study. The data include analysis of the appearance of all local tumors and do not

attempt to classify them into specific types, although fibrosarcoma appears to be the tumor seen in the majority of cases. Grüneberg[8] reports that no strain of mice has yet been described in which spontaneous tumors of the skin and subcutaneous tissue is common with any great incidence. No spontaneous tumors, except adenocarcinoma of

TABLE 3. GENETIC SYMBOLS AND THE PHENOTYPE OF THE MICE DISCUSSED IN THIS PAPER

Genetic symbol	*Phenotype*
B	black coat
b	brown coat
P	dark eye
p	pink eye
S	self
s	piebald
D	non-dilute (intense)
d	dilute
A	agouti
a	non-agouti
C	non-albino (colored)
c	albino
Se	long ear
se	short ear

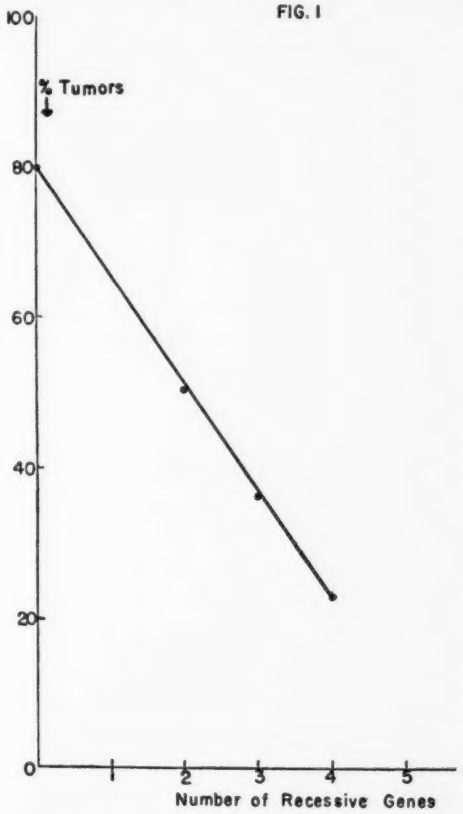


FIG. 1. Correlation between the relative number of recessive genes in the genotype of the mice studied and the incidence of tumor formation.

the mammary gland, have been obtained by Strong[38] in his colony of control animals for the strains used in the present work which have been observed over a period of many years. Therefore, we may exclude spontaneous tumors as a source of error in this investigation.

The mice were given a diet of nurishmix with an unlimited supply of water, and housed in a room with temperature controlled at 70-73° F. and humidity controlled at

50-60 per cent. Five or less mice were kept in each side of a double box and were not allowed to breed.

In addition to controlling the pedigree of the animals, the litter seriation phenomenon as shown by Strong[28] was taken into account. For this reason, only mice from the first, second, and third litters of a particular mating were used in the investigation. Furthermore, the lineage was selected toward early litters for several generations. This precaution offset any variability which might have appeared if animals of later litters had been used either as breeders or experimental animals.

TABLE 4. LATENCY PERIOD IN DAYS FOR ALL GROUPS OF MICE INVESTIGATED

	Genotype	*Groups*	*Median*	*Groups*	*Median*
male	SSDD	pBr	190 ± 11.5		
female			150 ± 9.5		
male	SsDd	F_{1a}	210 ± 15.3	F_{1b}	200 ± 8.8
female			187 ± 15.7		170 ± 5.4
male	SsDd	F_{2a}	216 ± 10.8	F_{2e}	210 ± 8.2
female			188 ± 24.2		191 ± 8.9
male	Ssdd	F_{2b}	228 ± 9.2	F_{2f}	225 ± 10.7
female			215 ± 11.8		220 ± 9.7
male	ssDd	F_{2c}	229 ± 13.9	F_{2g}	228 ± 10.5
female			214 ± 15.4		218 ± 7.6
male	ssdd	F_{2d}	245 ± 11.4	F_{2h}	235 ± 10.2
female			235 ± 13.4		225 ± 9.8
male	ssdd	I	240 ± 29.1		
female			235 ± 25.5		

RESULTS

The data obtained on the incidence of local tumors and the latent periods of the several strains of mice are given in Figure 1 and Table 4, respectively. There is no significant difference in the values for percentage of tumors and latency period medians in the mouse groups bearing the same number of recessive genes in their genetic makeup, whereas in the groups bearing different numbers of recessive genes the values are significantly different. The median result is probably a more reliable measure in this study and therefore has been used, since the median excludes the few mice that develop tumors at a very early age and those that do not develop tumors at all. In determining the probable error of the median, the formula used is:

$$\text{P.E.} = \frac{\text{average deviation quartiles } \frac{(Q_3 - Q_1)}{2}}{\sqrt{N}}$$

In this paper, following the example of Strong,[25] the term local tumor applies to all tumors that arise at the site of injection of methylcholanthrene. In contrast to Strong, however, who analyzed the effect of litter seriation on fibrosarcoma alone, these tumors include fibrosarcoma, epidermoid carcinoma, rhabdomyosarcoma, and a few carcinomas of the mammary gland. This classification is not the usual one, but is based on the genetic concept that the only manner by which a gene can be identified is by its effect upon the organism. Therefore, if there be any genetic factor in common to several or all neoplastic growths, it can be identified only by classifying all types of tumors together.

DISCUSSION

The process of carcinogenesis is one in which there seems to be three variables: (i) the genetic make-up of the tissues affected; (ii) the extragenetic environment, such as litter number, sex, age, hormone balance, etc.; and (iii) some physiological or pathological imbalance or irritation caused by an alteration in the tissue metabolism, either naturally or experimentally induced.

The evidence is accumulating that the appearance of a local tumor arising at the site of injection of methylcholanthrene is determined, to a great extent, by the constitutional state of the individual. This is, in turn, under genic control as well as of some other force as measured by litter seriation. Strong[21] expresses the opinion that the genes involved in local tumor susceptibility are probably few in number. He has found one of these to be in linkage relationship with the brown coat gene and another with the piebald gene. Maud Slye[14, 15] proposed that spontaneous cancer behaves as a simple Mendelian recessive. In addition, using well-pedigreed stocks but also, according to Little,[11] questionable thinking, she feels that the type of tumor as well as the location of tumor formation are likewise inheritable. Lathrop and Loeb[10] and Lynch[12] found cancer to behave as a Mendelian dominant. Reinhard and Candee[18] and also Kreyberg[9] have shown a longer latent period before tumor formation in the male, in contrast with the female. On the other hand, Branch[5] found no significant difference between C_{57} males and females.

The resistance of a strain is determined by the period of time elapsing between injection of the carcinogenic agent and the appearance of the tumor, i.e., the latent period, and the percentage of mice developing tumors. These factors are related to the amount of carcinogen used, the potency of the carcinogen, and the genetic uniformity or variability of the experimental animals. Strong[26] has shown recently that the litter number to which the

mice belong, i.e., the age of the mother at the time of birth of the mice, is an important factor in the length of the latent period, presumably due to extrachromasomal factors which influence the susceptibility to fibrosarcoma.

Andervont[3] has reported that the F_1 generation derived from mating C_3H to I strains and C_3H to Y strains were of intermediate susceptibility when compared with the susceptibility of the parent strains. Strong[23] has found similar results with other strains. In addition, he[33] established the following relationship amongst several strains in order of increasing resistance: black coat (*B*), brown coat (*b*), pink eye (*p*), pink eye brown (pBr), and I strains. It occurred to one of the writers that each succeeding strain of the group differed from the one directly above it by only one gene in its genetic make-up. Further, the gene is recessive to the one at the same locus of the strain immediately above on the curve of increasing resistance. Thus *b* strain differs from *B* strain only in having the recessive gene for coat color instead of the dominant one; *p* differs from *b* strain in having the recessive gene *p* for eye color instead of the dominant *P* gene; pBr strain differs from *p* strain in the gene for coat color, pBr having the recessive *b* gene. I strain (*ppbbssdd*) has the recessive genes *ssdd* instead of the *SSDD* genes of pBr.

Synthesis of these observations allows a relationship to be built and correlated with resistance to tumor formation by methylcholanthrene. The most likely answer to these facts seems to be that these recessive genes impart more resistance than their dominant alleles. In addition, the process seems to be an additive one. Therefore, a strain with two recessive genes has greater resistance than one with only one, etc. For that reason the I strain with four recessive gene loci more than the *B* strain should be many times more resistant to tumor formation.

The actual mechanism of the correlation between recessive genes and resistance is, of course, open to much speculation, but Strong[22] suggests one very plausible hypothesis. He has shown that a gene S^{fs} (susceptibility of fibrosarcoma) is in linkage relationship with the dominant black coat gene *B*. Arguing from this, we may postulate several genes similar to the S^{fs} gene which are linked to other genes, predominantly dominant ones. These *S* (susceptibility) genes should obey the same laws of Mendelian heredity as we know them (linkage and crossover) as others. In this hypothesis, recessive genes for coat color, eye color, etc. would be linked with recessive genes for resistance to fibrosarcoma (s^{fs}).

The present investigation undertook to test this hypothesis. In analyzing the results it can be seen that the F_1 generation is intermediate in susceptibility to that of the parental generations, which has also been shown by

others,[3, 23] and which is in accordance with the present hypothesis. The difference in latent periods between the F_{1a} and the F_{1b} strains is not statistically significant, probably due to the small numbers of animals involved.

In the backcross to the recessive, not only is there segregation in the backcross to four different classes of phenotypes and genotypes in the expected 1 : 1 : 1 : 1 ratio, but there is also the same segregation in tumor susceptibility. And, what is more significant, the various classes behave as expected from the hypothesis. Thus, F_{2a} and F_{2e} which are identical genetically with F_{1a} and F_{1b} (*SsDd*) have latent periods which are almost identical (the difference not being statistically significant). The F_{2b} and F_{2f}

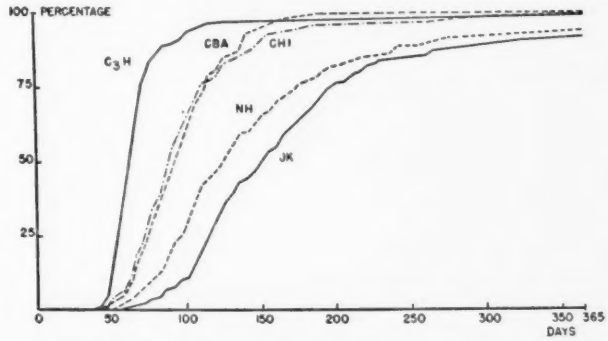


FIG. 2. Time from injection to appearance of tumors in five inbred strains (from Burdette and Strong[6]).

(*Ssdd*) classes which are intermediate to the F_1 and the I strains in respect to the number of recessive genes in the genetic make-up are found to be also intermediate in their latent periods. In the same fashion are the F_{2c} and F_{2g} (*ssDd*) classes the same. The F_{2d} and F_{2h} (*ssdd*) classes, identical with the I strain in genetic make-up, have latent periods very closely approximate to that of the I strain, again the difference not being statistically significant.

Thus we have succeeded in establishing several intermediate points in the resistance relationship among the several strains as determined by Strong[33] and discussed above, and have succeeded in establishing a workable hypothesis of the inheritance of tumor susceptibility and resistance.

An analysis of the literature shows that one may explain the greater susceptibility of one strain over another in many workers' series by the present hypothesis. Strong[22] reports the mutation of brown (recessive) coat color to one of black (dominant) with the concomitant large increase of

susceptibility to fibrosarcoma induced at the site of methylcholanthrene injection. Burdette and Strong[6] demonstrated relationships in several strains of mice as shown in Figure 2. The genetics of these strains are characterized in Table 5. Here again the series follows the general pattern of the relationship of resistance to the recessiveness (or number of recessive genes in the genetic constitution).

Andervont has done a great deal of work in experimental cancer genetics. His series of strains[2] together with their genetic make-up and resistance relationship is shown in Table 6. He found, as have many other workers in

TABLE 5. GENETIC MAKE-UP OF THE ANIMAL STRAINS ANALYZED BY BURDETTE AND STRONG[6]

Strain	*Genotype*
C_3H	*AABBCCDDPPSSSeSe*
CBA	*AABBCCDDPPSSSeSe*
CHI	*AABBCCDDPPSSSeSe*
NH	*AABBCCddppssSeSe*
JK	*aabbCCDDppSSSeSe*

TABLE 6. GENETIC MAKE-UP OF ANIMAL STRAINS ANALYZED BY ANDERVONT[2]

Strain	*Genotype*
C_3H	*AABBCCPPDDSSSeSe*
C	*AAbbCCppDDSSSeSe*
M	*aabbCCPPDDSSSeSe*
C_{57}	*aaBBCCPPDDSSSeSe*
A	*aabbccPPDDSSSeSe*
D	*aabbCCPPddSSSeSe*
I	*aabbCCppddssSeSe*

the past, that the C_3H strain of mice was very susceptible to tumors induced by carcinogenic hydrocarbons, and the I strain was very resistant. Between these extremes he found the C, M, C_{57}, A, and D strains in that order of relative increasing resistance to tumor formation. Inspection of the genotype relations reveals a general increase in the number of recessive genes as the resistance increases, in accordance with the present hypothesis.

What is the significance of the recessive tendency in the genetic control of resistance to tumor formation? It may mean the hereditary transmission of greater or lesser resistance is involved in a change in cell metabolism. Or it may mean that genes can control the production of an individual with a greater or lesser degree of resistance to malignant disease, or even to all disease. From the results of the present investigation and its apparent corroboration in the literature, the conclusion can be drawn that the resistance to cancer in experimental animals is at least partly associated with the cumulative recessive traits of the individual.

SUMMARY

1. A correlation between tumor resistance, as measured by the latency period and the percentage of animals acquiring tumors, and the number of

recessive genes in the genotypic make-up has been investigated, the tumors being induced with methylcholanthrene.

2. Evidence is presented which points to the fact that the particular recessive genes studied impart more resistance than their dominant alleles. In addition, the relationship seems to be an additive phenomenon, i.e., the more recessive genes in the make-up of the animal, the greater the resistance.

3. The results of this study are discussed in light of findings of various other investigators, with which they seem to be in accord.

4. A speculative hypothesis as to the mechanism is presented and discussed.

REFERENCES

1 Andervont, H. B.: The production of tumors in mice of strains C_3H and Y by dibenzanthrene and methylcholanthrene. Pub. Health Rep., Wash., 1938, *53*, 229.

2 Andervont, H. B.: Susceptibility of mice to spontaneous, induced, and transplantable tumors. Pub. Health Rep., Wash., 1938, *53*, 1647.

3 Andervont, H. B.: The incidence of induced subcutaneous and pulmonary tumors and spontaneous mammary tumors in hybrid mice. Pub. Health Rep., Wash., 1938, *53*, 1665.

4 Boyland, E. and Warren, F. L.: The induction of tumors by methylcholanthrene in two strains of mice. J. Path. Bact., 1937, *45*, 171.

5 Branch, C. F.: Dibenzanthracene tumors in controlled strains of mice. Am. J. Cancer, 1926, *26*, 110.

6 Burdette, W. J. and Strong, L. C.: The inheritance of susceptibility to tumors induced in mice. I. Tumors induced by methylcholanthrene in five inbred strains of mice. Cancer Res., 1943, *3*, 13.

7 Gardener, W. U.: Unpublished data.

8 Grüneberg, H.: *The genetics of the mouse*. Cambridge University Press, 1943.

9 Kreyberg, L.: *A symposium on cancer*. The genetic and constitutional aspects of spontaneous and induced tumors. Madison, Wisconsin, The University of Wisconsin Press, 1938.

10 Lathrop, A. E. C. and Loeb, L.: Further investigations on the origin of tumors in mice. J. Cancer Res., 1916, *1*, 1.

11 Little, C. C.: Evidence that cancer is not a simple mendelian recessive. J. Cancer Res., 1928, *12*, 30.

12 Lynch, C. J.: Study on the relation between tumor susceptibility and heredity. J. Exp. M., 1924, *39*, 481.

13 Reinhard, M. C. and Candee, G. F.: Influence of sex and heredity on the development of tar tumors. Am. J. Cancer, 1932, *16*, 640.

14 Slye, M.: The inheritance behavior of cancer as a simple mendelian recessive. 21st report. J. Cancer Res., 1926, *10*, 1.

15 Slye, M.: Heredity as determining the type and site of cancer and the age at which it occurs. Am. J. Path., 1941, *17*, 655.

16 Strong, L. C.: Genetic indications correlated with the transplantation of cancerous tissue. J. Hered., 1924, *15*, 355.

17 Strong, L. C.: General considerations of the genetic study of cancer. J. Cancer Res., 1926, *10*, 219.

18 Strong, L. C.: The genetic appearance of spontaneous carcinoma of the mammary gland in the C$_3$H mice. Am. J. Cancer, 1935, *25*, 599.

19 Strong, L. C.: A genetic analysis of the induction of tumors by methylcholanthrene with a note on the origin of the NH strain of mice. Am. J. Cancer, 1940, *39*, 347.

20 Strong, L. C.: The origin of some inbred mice. Cancer Res., 1942, *2*, 531.

21 Strong, L. C.: Genetic analysis of the induction of tumors by methylcholanthrene. XII. The effects of selection toward resistance. Yale J. Biol., 1946, *18*, 145.

22 Strong, L. C.: Linkage and crossing over between black pigmentation and susceptibility to induced fibrosarcoma in mice. Science, 1946, *103*, 554.

23 Strong, L. C.: A genetic analysis of the induction of tumors by methylcholanthrene. XIII. Mutation from brown to black with a concomitant increase of susceptibility to fibrosarcoma. Yale J. Biol., 1946, *18*, 359.

24 Strong, L. C.: Observations on the genetic nature of gastric cancer in mice. Surg. Gyn. Obst., 1947, *84*, 727.

25 Strong, L. C.: Further observations on the genetic nature of gastric cancer in mice. J. Nat. Cancer Inst., 1947, *7*, 305.

26 Strong, L. C.: A new influence on chemically induced sarcomata. Science, 1948, *108*, 688.

27 Strong, L. C.: A new theory of mutation and the origin of cancer. Yale J. Biol., 1949, *21*, 293.

28 Strong, L. C.: The induction of mutations by a carcinogen. Brit. J. Cancer, 1949, *3*, 97.

29 Strong, L. C.: The control of survival time in mice bearing methylcholanthrene-induced fibrosarcomas. Science, 1950, *111*, 381.

30 Strong, L. C.: Litter seriation and the invasion of fibrosarcomas in mice. Yale J. Biol., 1950, *22*, 303.

31 Strong, L. C.: A sex differential for chemically induced fibrosarcoma associated with litter seriation. Brit. J. Cancer, 1950, *4*, 315.

32 Strong, L. C.: Test of correlation between pink-eye gene and susceptibility to induced fibrosarcomas in mice. Cancer Res., 1951, *11*, 42.

33 Strong, L. C.: Unpublished data.

34 Strong, L. C. and Hollander, W. F.: Effects of methylcholanthrene in pregnant mice. J. Nat. Cancer Inst., 1947, *8*, 79.

ALLAN V. N. GOODYER*
ERNEST ROSENTHAL†
CARL A. JAEGER‡

Departments of Medicine and Ophthalmology, Yale University School of Medicine

THE CLINICAL EVALUATION AND MANAGEMENT OF HYPERTENSION§

Part I. Evaluation of the Definition, Etiology, and Prognosis of Hypertension (Goodyer)

Part II. Evaluation of Fundoscopic Findings in Hypertension (Rosenthal)

Part III. Medical Treatment of Hypertension‖ (Jaeger)

In the present review, an attempt is made to crystallize, from the extensive and often contradictory literature on hypertension, a rational approach to the management of the hypertensive patient.

On the basis of criteria regarding etiology and prognosis outlined in Parts I and II, a plan of medical treatment is presented in Part III which is particularly concerned with the use of the newer "anti-hypertensive" drugs. Some of the results of drug therapy are summarized from the literature as well as from our own clinical experience with 56 patients.

PART I. EVALUATION OF THE DEFINITION, ETIOLOGY, AND PROGNOSIS OF HYPERTENSION

I. EVALUATION OF THE SIGNIFICANCE OF AN APPARENTLY HIGH BLOOD PRESSURE READING

There are several points which must be considered before a blood pressure reading can be classified as "normal" or "abnormal" for a given patient:

a. *The method of measurement.* Auscultatory methods for measuring blood pressure underestimate direct methods by increasing increments as

* Assistant Professor of Medicine; Established Investigator of the American Heart Association.
† Clinical Instructor in Ophthalmology.
‡ Trainee of the National Heart Institute.
§ Supported in part by a grant from the American Heart Association.
‖ The drugs used in this study were supplied by E. R. Squibb and Sons, Wyeth Laboratories, Burroughs Wellcome, Ciba Pharmaceutical Products, Riker Laboratories, Inc., Merck and Co., and Smith, Kline and French Laboratories.
Received for publication May 13, 1955.

the level of blood pressure rises.[130] Variations in the relation between the arm and sphygmomanometric cuff contribute further error to the determination as does the uncertainty as to which phase of the Korotkoff sounds is acceptable as the truest indication of the diastolic blood pressure.[9, 101, 130] (Recent evidence favors use of the muffling of sounds rather than their disappearance.[101]) In addition, the position of the patient has a variable effect on the blood pressure which is of particular importance in patients under treatment with hypotensive drugs. Even without medication, the blood pressure of the standing patient may be as much as 25/10 mm.Hg lower than that of the same individual when supine.

b. *The definition of "normal blood pressure."* The limits of "normal" blood pressure remain ill-defined.[24] On the one hand, upper limits of normal have been based on statistical averages of mixed groups which include unknown numbers of hypertensives.[102] According to such data, more than 50% of patients past the age of 50 years have blood pressures over 140/90. On the other hand, the value of about 140/90 has been set as the upper limit of normal on the basis of insurance groups from which higher values tend to have been pre-excluded.[74] Until better data, or more practical and safe methods of controlling blood pressure, are available, it may be best to consider values between 140/90 and the higher averages advocated by Master as "suspicious," but unproven hypertension.

c. *Physiological variations of the blood pressure.* The normal slight lability of the blood pressure is exaggerated in anxious patients so that diastolic as well as systolic hypertension may be present with excitement, or during initial blood pressure determinations, and may be absent in most subsequent measurements. Some of these "hyper-reacting" individuals may be more than usually likely to exhibit later hypertension.[62, 63] In any event, many determinations of the blood pressure, under as restful conditions as possible, may be necessary in some patients to establish the usual range and average value of their blood pressure. Such data are best obtained as unobtrusively as possible in order to avoid overemphasizing the importance of the level and variations of blood pressure to the patient.

d. *Diastolic vs. systolic values.* Diastolic elevation of blood pressure, with which systolic elevation is usually associated, is of primary importance in relation to hypertensive vascular disease. An elevated systolic with normal or low diastolic value is not an indication of the more serious type of hypertension,* but may be associated with a variety of circumstances in which

* Except when severe aortic insufficiency is superimposed on hypertension which would otherwise be of the diastolic type.

stroke volume or diastolic "run-off" is increased, or in which the elasticity or capacity of the large arteries is diminished. Systolic hypertension may be found with the high stroke volume of excitement, severe anemia, hyperthyroidism, bradycardia, marked peripheral vasodilatation, aortic insufficiency, and A-V shunts; or with aortic abnormalities such as coarctation, arteriosclerosis and obliterative endarteritis. (The latter process may, by involving the renal artery, cause more serious diastolic hypertension, as indicated below.)

II. ETIOLOGICAL EVALUATION

The finding of persistent *diastolic* hypertension imposes an obligation on the part of the physician to search, as briefly or as extensively as seems warranted in each instance, for one or more of the remediable etiological factors which may be involved in producing the hypertension. However, it is important to avoid overemphasizing to the patient, by an extensive investigation, the seriousness of an illness for which no truly remediable cause may be found and for which the available nonspecific therapy may well be unsatisfactory, or even unnecessary.

In general the more obviously serious the disease is, the more it warrants diligent search for a specific etiology, but at the same time it must be borne in mind that hypertension, due at first to a completely remediable primary cause (e.g., an ischemic kidney), may eventually become self-perpetuating even if the primary cause is removed. Early diagnosis of such a primary cause is therefore very important.

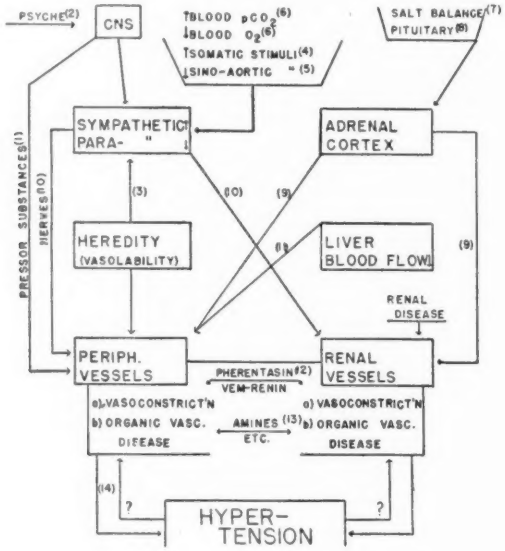
Diagram 1 illustrates the interplay of some of the physiological and pathological mechanisms which have been implicated in the production of hypertension. A detailed review of the experimental data upon which the diagram is based would be outside the scope of this presentation. The small numbers have therefore been included in order to indicate references which document the relations that are indicated in the diagram and summarized as follows:

a. The hemodynamic basis of hypertension is (with the exception of aortic coarctation) arteriolar obstruction to blood flow, caused by vasoconstriction and organic vascular disease (Diagram 1, No. 14), the cardiac output remaining normal. The question (see Diagram 1) of whether hypertension may, in itself, cause vascular disease is discussed in subsequent pages at length.

b. The renal vessels have been set aside from other peripheral vessels because of the experimental and clinical evidence indicating their particular importance to the problem of hypertension.

c. Part of the arteriolar abnormality may in many cases arise as a result of imbalance or excesses of depressor and pressor substances circulating in the blood. These have been identified as originating in the brain (Diagram 1, No. 1), the kidney (Diagram 1, Nos. 12 and 13), the liver (Diagram 1, No. 11), the endocrine organs (Diagram 1, Nos. 7, 8 and 9), and from unknown sources (Diagram 1, No. 12).

DIAGRAM I. SCHEMA ILLUSTRATING THE ETIOLOGY OF HYPERTENSION



Legend: The relations indicated in the diagram are labeled with numbers which refer to references listed alphabetically at the end of this review, as follows:

(1) Page, 1951
(2) Weiss, 1942; Binger, *et al.*, 1945; Gressel, *et al.*, 1949
(3) Weiss, 1942; Hamilton and Pickering, 1954
(4) Burch, *et al.*, 1942; Brust, *et al.*, 1951
(5) Heymans, *et al.*, 1951; Kezdi, 1953
(6) Von Euler and Liljestrand, 1946
(7) Kempner, 1948; Hatch, *et al.*, 1954
(8) Handler and Bernheim, 1950; Findley, 1949
(9) Selye, 1950; Perera, 1950; Merrill, 1952
(10) Whitelaw and Smithwick, 1951
(11) Zweifach and Shorr, 1948
(12) Schroeder and Olsen, 1950; Corcoran, *et al.*, 1951
(13) Waters, 1948
(14) Bradley, 1948

d. Neurogenic factors may play a rôle in the arteriolar vasoconstriction (Diagram 1, No. 10) as a result of a variety of stimuli (Diagram 1, Nos. 2-6).

e. The arterioles themselves may change in morphology or in reactivity to humoral pressor or neurogenic factors as a result of aging, heredity, or endocrine influences (Diagram 1, No. 9).

Many of the mechanisms outlined in the diagram are not susceptible to clinical evaluation. However, appropriate diagnostic procedures may be directed toward the following diseases which may give rise to hypertension:

1. *Renal disease.* Urinalysis, urine cultures, urine function tests (PSP, NPN, concentration test, inulin and PAH clearances), and the I-V pyelogram, correlated with the clinical history, will fairly well identify *glomerular nephritis, pyelonephritis,* and *polycystic kidneys.*[44] Although a good case can be made for a close relationship between pyelonephritis and associated hypertension,[112] convincing statistical evidence to the contrary has been presented.[121] Antibiotic treatment of active pyelonephritis may prevent further renal damage but is quite unlikely to eliminate the associated hypertension. The finding of polycystic kidneys usually warrants some shift in emphasis from the problem of hypertension to that of gradually progressive renal failure. Although 75% of adult patients with this disease have hypertension, only about 5% have more than grade II retinopathy (see Part II below) and only 30% die as a result of hypertension or its effects.[94] *Unilateral renal disease* may be particularly suspected if the hypertension is severe, of recent onset, and in a young or elderly patient.[80] If the initial renal examination yields further evidence of this possibility, retrograde urography, aortography, and, finally, unilateral nephrectomy may be warranted in view of the scattered reports of the rare cure of severe hypertensive vascular disease by extirpation of unilateral renal disease—particularly pyelonephritis, hydronephrosis, and partial renal arterial obstruction.[27, 80, 96, 106, 121] It is well to realize that hypertension related to disease of one kidney not only is quite rare, but also is persistent after nephrectomy (i.e., is already self-perpetuating by the time of nephrectomy) in 50-75% of cases.[80, 121] On this basis, only urologic indications for nephrectomy (especially the finding of one essentially nonfunctioning kidney in the presence of good contralateral function) are accepted by some writers,[121] although in several cases hypertension has been relieved by removal of an ischemic, but still functioning, kidney.[27, 64, 106]

2. *Adrenal disease.* Secretions of the *adrenal cortex* appear to be necessary for the preservation of normal vascular reactivity[140] and for the maintenance of normal blood pressure.[17] Hypotension is a cardinal symptom

of Addison's disease. Hypertension is a frequent manifestation of the classical Cushing's syndrome, as well as of the "pseudo-Cushing's" syndrome in women described by Schroeder,[109] and is occasionally seen during DOCA or ACTH therapy (Cortisone being a less frequent offender), particularly in patients with antecedent hypertensive tendencies[45, 128] and renal disease.[39] Hypertension in these circumstances may be much ameliorated or eliminated by salt restriction, and even more effectively by removal of the source of the cortical hormones, where this is possible. The *adrenal medulla* is normally concerned with blood pressure only under "emergency" conditions when its secretion, containing predominantly epinephrine (80% vs. 20% norepinephrine), causes elevation of the systolic pressure with very little change in the diastolic pressure.[42] However, rare pheochromocytomata (usually of the adrenal medulla) may cause intermittent or continuous diastolic hypertension associated with a clinical picture dependent, at least in part, on the relative proportions of epinephrine and norepinephrine in their secretions. The hypertension is often severe and may occur with normal heart rate, blood sugar, and basal metabolic rate, particularly—but not necessarily—when norepinephrine predominates in the tumor. The most direct tests for pheochromocytomata, i.e., the assay of blood and urine for epinephrine and norepinephrine, are not ordinarily available, although promising chemical methods for screening urines for these compounds have been recently described.[48] However, in spite of occasional false positive and negative results, several practical pharmacological tests are useful in detecting pheochromocytomata in selected hypertensive patients.[16] Present preference seems to be for the *Regitine test*[26] in cases of persistent hypertension, because of the absence of severe side reactions seen with benzodioxane, and for the *mecholyl* test[25] (with atropine) in cases of paroxysmal hypertension seen during a normotensive phase, because of the greater incidence of side reactions and false positive results with the histamine test. In cases showing distinctly positive tests by two methods or on two occasions, examination of the adrenal area by means of I-V pyelograms and/or presacral air studies[14] may be confirmatory. Although the finding of a pheochromocytoma is extremely important for the patient so involved, the rarity of the disease is such that a great number of negative tests in patients with persistent hypertension must, on the average, be performed before a pheochromocytoma is found. This small "return," the nuisance (to say nothing of the possible psychic trauma to the patient) of an occasional false positive test, and the knowledge that hypertension may persist (in 7 of 12 cases in one series[41]) after operative removal of the rare tumor which is found, all raise some doubt as to the usefulness of using the pharmacologi-

cal tests in hypertensives in whom the possibility of pheochromocytomata is not suggested on clinical grounds[14] (crises, elevated BMR, glycosuria, severe sweating, "paroxysmal nephritis"[20]), or in whom the hypertension is not severe.

3. *Coarctation of the aorta,* another uncommon cause of hypertension, is nevertheless to be carefully considered in every case because of its potential remediability. This possibility can be evaluated by the simple procedure of palpating the pulses (and, if necessary, by measuring the blood pressure) in the lower extremities. Several diseases which also diminish or eliminate the femoral pulses, such as obliterative aortic arteriosclerosis (Leriche's syndrome) or dissecting aortic aneurysm, should cause no confusion, since they have very different clinical backgrounds. Ribnotching and a characteristic aortic cleft (at the site of coarctation) in the ordinary chest film are pathognomonic.

4. *Toxemia of pregnancy* is characterized by a rising diastolic blood pressure, increasing edema, and albuminuria in the young, previously normotensive, primigravid patient during the 7th-8th month of pregnancy.[34] In patients with pre-existent, persistent hypertension, indicated by history and by the presence of vascular changes in the fundi, toxemia tends to be more frequent (40-50%), earlier in occurrence (4th-5th month), and more severe.[21] Many mild hypertensives do well during pregnancy, and appear to suffer no increase in their vascular disease. However, if progressive toxemia occurs for more than four to five weeks, subsequent persistent hypertension (in patients previously normotensive), or prolonged exacerbation of pre-existent hypertension is likely.[21, 34] Therefore, therapeutic abortion for severe hypertension during the first trimester, and intensive medical therapy, including salt restriction and the use of anti-hypertensive drugs (see Part III, below), for severe toxemia or eclampsia in the later months of pregnancy, are widely recommended.[3, 32, 33]

5. *Other unusual diseases* which may be associated with hypertension are listed below. Their recognition will tend to shift the emphasis of prognosis and management from the hypertension to the primary disorder itself.

(a) Periarteritis nodosa
(b) Lupus erythematosis
(c) Bulbar poliomyelitis
(d) Brain tumor and increased CSF pressure
(e) Tabetic crises
(f) Porphyria
(g) Multiple myeloma.

III. PROGNOSTIC EVALUATION

Most cases of hypertension have either no identifiable etiology, or are associated with disease (usually renal) which is not primarily remediable. The problem of management in each case then involves repeated re-evaluation of the prospective morbidity and mortality of untreated as compared with treated disease.

The prognosis of untreated hypertension in each patient may be estimated, with only fair correctness, by a study of the initial characteristics of the disease and the course of associated vascular disease in the CNS, heart, and (especially) ocular fundi and kidneys. The results of the study can then be compared (grossly, or by an appropriate "scoring" system) with similar data reported for large series of cases in the literature.[5,29,49,55,68,85,87,95,108]

The following *initial characteristics* favor the likelihood of a more benign course: age of patient more than 50, female sex, negative family history, relation to menopause, asymptomatic onset, prior duration for more than 10 years, diastolic values less than 120 mm.Hg, lability, absence of recent progression, absence of vascular disease. Specific evidence of lability may be given by spontaneous fall of the pressure to low or even normal levels when initial anxiety of the patient has been relieved, or during an amytal sedation test.

Data useful in estimating the extent of organic vascular disease may be outlined as follows:

1. *Fundoscopic changes* (see Part II, below).

2. *Renal function*—initial examination of the kidneys for the *presence* of disease has been described above in discussing primary renal disease. With respect to the problem of prognosis, an evaluation of the *extent* of renal impairment is also very important. Marked functional impairment usually indicates severe, progressive disease with a poor prognosis, and the possibility of a developing malignant phase. The PSP test (indicative of renal tubular function and blood flow), and the urine concentration test (indicative of more specific tubular functions) may indicate renal impairment long before it becomes evident via urinalysis or elevation of the NPN.[44] Studies of the clearances of inulin and PAH, etc., may provide even earlier and more exact indications of the disproportionate reduction of renal blood flow (as compared with glomerular filtration) characteristic of severe hypertensive disease, but they are too burdensome to be applicable to the ordinary case of hypertension.[10,28,44] Percutaneous renal biopsy is potentially much more informative,[50] but has not yet been established as an entirely safe and truly valuable procedure for other than a few specially selected cases.

3. *The heart.* Left ventricular hypertrophy (as indicated by the electrocardiogram and chest film) is usually an indication of longstanding disease; congestive heart failure (often preceded by a diastolic apical gallop) and coronary disease (indicated by the electrocardiogram, and a history of angina or myocardial infarction) are particularly indicative of a serious prognosis. On the other hand, marked hypertension may persist for many years without these evidences of cardiac damage.

4. *The CNS.* A cerebral vascular accident in a hypertensive patient implies probable cerebral arterial or arteriolar disease and portends further cerebral vascular difficulties. Hypertensive encephalopathy, characterized by clouding of the sensorium or convulsions in the presence of extreme elevation of the blood pressure, usually indicates a very serious prognosis in the absence of a specific remediable cause for the hypertension. However, it is not necessarily associated with cerebral vascular disease, may have no neurological sequellae, and is therefore potentially completely reversible. Hypertensive encephalopathy in experimental animals is characterized by patchy increases in cerebral capillary permeability due to severe vasospasm.[19] This pathogenesis seems more reasonable than the hypothesis that the elevated arterial pressure "breaks through" the arteriolar resistance to be transmitted to the post-arteriolar vascular bed.[82] Encephalopathy may respond dramatically to antihypertensive drugs, particularly in the absence of uremia, probably by direct relief of vasospasm. The malignant phase of hypertension, in which encephalopathy is common, is of special import because it presages death within a year.[108] It is characterized by extreme diastolic hypertension, pathognomonic papilledema associated with severe retinopathy, and rapidly progressive renal and cardiac impairment.

A review of the above clinical data for a given hypertensive patient should, ideally, allow: (a) identification of the patient with one of several grades or groups of hypertensive disease for which the average prognosis is known; (b) comparison of this prognosis with that of the same grade of disease subjected to each of the available methods of therapy; (c) selection of that form of therapy which holds the most promise for improving the prognosis of the untreated disease.

In practice, only part of this complete evaluation can be made. Published data concerning prognosis of various groups of untreated and treated disease based primarily on fundoscopic findings (see Part II, below), as well as on "scoring" systems, are summarized in Table A. A representative "scoring" system, used in this clinic, is summarized in Table B. Each listed adverse, abnormal clinical finding is given a "severity index" from one to four depending on the degree or innate seriousness of the abnormality. The

TABLE A. MORTALITY AND RESULTS OF VARIOUS TYPES OF TREATMENT OF HYPERTENSIVE PATIENTS, GRADES I-IV. FIGURES REPRESENT PERCENTAGES OF ALL PATIENTS IN EACH CATEGORY

Mortality	*Control (untreated)*	*Rauwolfia group*	*Veratrum group*	*Apresoline*	*Methonium compounds*	*Rauwolfia + Methonium*	*Apresoline + Methonium*	*200 mg. Na (or rice) diet*	*Sympathectomy*	*Sympathectomy + adrenalectomy*
Grade I–II 1 yr.	5								5	7
3 yr.	10–20								7–11	
5 yr.	20–35								15	10
Grade III 1 yr.	30								10	11
3 yr.	20–70						13		25–30	
5 yr.	50–80								40	22
Grade IV 1 yr.	80				18			18	25	38
3 yr.	55-95				42		25		40–55	
5 yr.	85–99								50	31
Sustained fall, blood pressure > 20 mm. Hg (all grades)	6–25	32–68	10–50	10–44	47–84	79	64–85	10–60	28–67	46
All grades: Prolonged improvement of:										
Headache	0–25	70–90	30	20–50	84	74			54–81	
Retinopathy	0–8	0		20	25	80		40	41	45
Decr. renal func.	0	0–10		0–8	20	25		62	29	
Angina		50	10		20	44			60	
CHF		20–33		40	57	45		55	42	
Enl. heart		0-3		20	5	3		38–60	15	45
Mild toxicity		60	80	40	50	50		60	50	
Mortal toxicity		<1	<1	<1	1	<1	3	8	9	25
Tolerable Rx		85–95	20–40	40–75	40–60	75–85	80	10–25	.....	..

(For documentation of these figures, see refs. no. 22, 37, 50, 61, 65, 69, 72, 78, 100, 110, 114, 115, 120, 122, 124, 129, 136, 138.)

total "score" for the patient at any time in the course of his disease is derived by totalling the "severity indices." For purposes of reference to other data, four ranges of "scores" are compared with equivalent terms or numerical grades now in common use in the literature. The data of Tables A and B provide some gross statistical basis for "clinical judgment" concerning the choice of management for the individual patient (see Part III, below). However, the evident gaps and inadequacies of the data, and the

TABLE B. CRITERIA FOR THE ESTIMATION OF THE SEVERITY OF HYPERTENSIVE VASCULAR DISEASE

Severity index	1	2	3	4
Diast. pressure	96–110	111–125	126–140	>140
Duration BP		2–5 yrs.	> 5 yrs.	
Fundi	I	II	III	IV
CVA			*	
LVH (ECG or x-ray)		*		
Congestive failure			mild	severe
Coronary disease		angina	infarct	
PSP (2°)%		40–60	20–40	<20
NPN			41–60	>60
Albuminuria	1+		2–3+	4+

Total score = sum of individual severity indices for each category.

Total score	*Equivalent Term*	*Approx. grade (Smithwick)*
1–7	Mild	I
8–13	Moderate	II
14–20	Severe	III
21 and over	Malignant	IV

great individual variability of the disease in individual cases, allow the clinician to accept such prognostic evidence only with the greatest caution and with moderate (but not blinding) scepticism.

The choice of treatment by "anti-hypertensive" agents also involves an evaluation of the validity of the implicit assumption that hypertension is itself productive of vascular disease. Against this assumption is the evident discrepancy between the *degree* of hypertension and the *extent* of the associated vascular disease. Patients with marked hypertension of unknown etiology, or due to aortic coarctation, may exhibit no evidence of vascular disease for many years,[47, 87] whereas (but this is rare) the vascular disease of "malignant" hypertension may rapidly progress in spite of the return of the blood pressure to normal values.[91] Furthermore, vascular lesions can be

produced in animals by agents such as alylamine under conditions where primary hypertension is avoided.[134]

However, there is increasing evidence which favors the view that hypertension may, in itself, cause arteriolar disease:

1. Renal biopsies indicate the absence of renal vascular disease during the early phases of essential hypertension.[15, 59]

2. Neither pulmonary vascular disease nor pulmonary hypertension occur in essential hypertension[9]; pulmonary hypertension due to other causes is commonly attended by pulmonary vascular disease.[46]

3. The vasculature of the unilateral Goldblatt kidney, which is protected from systemic arterial hypertension by the constricting clamp, escapes injury, whereas vascular disease is found in the "exposed" contralateral kidney.[40] Human case reports confirm this experimental observation.[27, 39]

4. Coarctation of the aorta, which causes initially remediable hypertension, may lead eventually to fixed hypertension (in 9 of 80 cases in one series[52]), associated with vascular disease.[93]

5. Hypertensive crises produced in dogs with sudden colloid infusions and with epinephrine cause severe arteriolar lesions resembling those of the malignant phase of essential hypertension.[135]

6. Unilateral renal disease, both in man and in the experimental animal, may cause hypertension which is ultimately associated with contralateral renal vascular disease.[27, 108]

7. Increasing evidence is accumulating of the amelioration or arrest of the course of vascular disease in some hypertensive patients by means of hypotensive agents which are not known to have primary effects on metabolism or the peripheral vasculature.

These observations, although not without objections (concerned with the possibility that an unrecognized primary "metabolic" abnormality may cause various mixtures of hypertension and arteriolar disease), justify the search for more effective and practical methods of blood pressure control. In addition, even the presently available measures are useful or may affect prognosis in ways which are not related to the prevention of vascular disease:

1. By providing an anxious patient (and his physician) with the reassurance that "something logical is being done," in a situation which may appear (sometimes for good reason) to portend serious disease.

2. By relief of distressing symptoms such as headache and irritability.

3. By lightening the work load of the heart, particularly when failure is

present or imminent, and relieving pulmonary engorgement in acute pulmonary edema.

4. By controlling hypertensive crises such as encephalopathy and eclampsia or pre-eclampsia.

These measures, with particular reference to drug therapy, are discussed in detail below (Part III).

PART II. EVALUATION OF FUNDOSCOPIC FINDINGS IN HYPERTENSION

The eye is the window in the human body where the vascular system at the arteriolar and precapillary level can be directly visualized. Much attention has therefore been paid to the vascular changes in the ocular fundus in hypertension, which when correlated with clinical and laboratory findings are of great importance in the estimation of prognosis. Photography, particularly stereophotography, of the fundus has been used in this clinic not only to evaluate the vascular changes present, but also to follow their development and course.

NORMAL ANATOMY OF THE RETINAL VASCULATURE

Wagener and his associates[132] have emphasized the importance of a thorough knowledge of the many variations of the normal eyegrounds. Friedenwald[85, 86] has clearly described the anatomical structure of the retinal vessels of various sizes and has classified the pathological changes which characterize each vessel type. The central artery, as it emerges from the optic disc, resembles arteries of similar size in many other organs. The intimal endothelial layer lies directly on the well-formed internal elastic lamella and the muscular coat is well developed. As the vessel passes forward, profound changes occur: the elastic lamella thins out and disappears after the first or second bifurcation, while the muscular coat is interrupted in increasingly wide gaps after a distance of about one disc diameter from the disc. With the exception of the retinal vessel near the disc, the visible vascular tree is arteriolar in character, the major branches of both arterioles and venules coursing at the level of the nerve-fiber layer. The precapillaries, however, can be divided into two groups: (i) the superficial group leading to capillaries in the nerve fiber layer; and (ii) the deep group leading to capillaries in the boundary plane between the inner nuclear and outer plexiform players. In general, the caliber of the retinal vessels narrows toward the periphery, most of the step-wise change being at the points of branching. The size of a branch is normally related to the size of its parent vessel in a ratio of 8: 10, or at most 7: 10. The choroidal circulation is made up of large vessels which lie near the sclera and a network of capillaries near

the retinal border. At the equator of the choroid, there is a rich anastomosis between the anterior and posterior arterial groups. Ashton has shown[3] that the choroidal circulation can be completely injected through a single anterior or posterior ciliary artery, even if one artery is severed before the injection. He suggested that localized lesions may occur in this circulation by leakage of blood or exudate with compression of adjacent choroidal vessels.

CLASSIFICATION OF FUNDOSCOPIC PATHOLOGY DUE TO HYPERTENSIVE DISEASE

Several classifications are widely known and used, the more popular being that of Keith, Wagener, and Barker[68] in which the fundus changes are correlated with the clinical findings, or the classification of Wagener, Clay, and Gibner[132] which limits itself to a very detailed description of retinal changes. Scheie[107] has recently outlined a very useful classification which emphasizes the differences between *hypertensive* (*vasospastic*) and *arteriolosclerotic* abnormalities, and which lends itself to reproducibility among several observers. Whatever method is used, certain vascular changes are recognized universally as being vasospastic and associated with hypertension per se:

1. Angiopathy—changes of the retinal vessels
2. Retinopathy—changes of the retina itself
3. Neuropathy—changes of the disc.

1. *Angiopathy.* In the early stages of hypertension the retinal arterioles may appear normal or even slightly dilated either because the retinal vessels share less in the generalized increase in arteriolar resistance which occurs, or because a change of the terminal arterioles cannot be appreciated ophthalmoscopically. In later phases of hypertension, irregularities (spasms) of the vessel walls are noted which may or may not be superimposed upon a more generalized narrowing. The latter is said to be characteristic of the occasional renal hypertension of elderly patients due to atherosclerosis of the renal arteries,[86, 88] and is said to correspond in degree with the severity of the hypertension in such individuals.

2. *Retinopathy.* In severe hypertensive disease, damage to the capillary wall and tissues of the retina results in extravasations and infarctions. Flame-shaped hemorrhages, localized exudates (of the "cotton-woll" variety), and edema so diffuse as to cause retinal detachments may be evident. In the macular region, the accumulation of fluid between the radially distributed Henle's fibers is the basis of the *"macular star"* (stellate figure), which, however, is not pathognomonic of hypertension occurring in other

pathological conditions. "Cotton-wool" patches about one-fifth the size of the disc may occur in the optic disc and in the region of the superficial capillary net, as a result, probably, of terminal arteriolar spasm.[85, 88] On section, these disc-shaped spots reveal a thickened nerve-fiber layer which contains globular bodies called "cytoid bodies."

3. *Neuropathy.* When edema involves the optic nerve, it obliterates the margins of the disc and the physiological cup, and causes the nerve head to protrude. This finding is commonly associated with "hypertensive encephalopathy."

As a consequence of long-standing hypertension, morphological residua may become apparent. Hyaline material is deposited under the vascular endothelium as far as the capillary system. The separated muscle fibers appear as crescentic clumps and present the picture of hyaline swelling. When fulminant, the subendothelial swelling may be accompanied by necrosis of the endothelial layer. These changes of *arteriolar sclerosis* cause a different set of ophthalmoscopic findings than those described above as being manifestations of hypertension per se:

1. *Changes of the arteriolar light reflex*

(a). *Widened arteriolar light reflex.* Thickening of the arteriolar wall makes the latter a more efficient reflector and therefore widens and brightens the light streak reflected from the vessel.

(b). *"Copper wire" arterioles.* Further widening of the light reflex is combined with the redness of the underlying blood column.

(c). *"Silver wire" arterioles.* The vessel wall is so dense that the blood column is obscured. The arteriole looks like a white cord.

2. *Changes of the arterio-venous crossings.* At these crossings, the arterioles and venules have a common anchorage because of a common adventitia. Normally, the venule passes undeviated closely over or under the arteriolar branch. As a result of arteriolar sclerosis the venule may be compressed as it crosses the arteriole, or may be deflected laterally so as to produce an abnormal, right-angle crossing, or an S- or U-shaped distortion. The vein may have the appearance of an arch or hump called a *Salus' Sign* if it passes in front of a sclerotic arteriole. The degree of compression is commonly graded I-IV. When Grade III, the venular column is partially obscured and appears tapered on each side of the crossing; when Grade IV, there is interference with the venous return and peripheral distention of the venule (*Gunn's Sign,* or "banking").

3. *Vessel tortuosity.* Loss of elasticity, thickening and lengthening cause increased tortuosity of both arterioles and venules.

4. *Choroidal changes.* These have been somewhat neglected in the literature concerning hypertension, probably because of their predominantly peripheral visualization in the fundoscopic examination. They are more often seen in the presence of severe hypertension, are ascribed to vascular sclerosis in the choroid, and are commonly associated with neuroretinopathy, though not necessarily so. In our experience, they have indicated a bad prognosis for the patient. They are evident as pigmentary changes visible in the choroid, through the peripheral retina, and are classified by Duke-Elder[23] as follows:

(a). Pale yellow or reddish plaques surrounded by pigmentary deposits.

(b). Black, isolated flecks of pigment with bright red or yellow halos (*Elschnig's spots*).

(c). Chains of pigmented spots arranged like a string of beads along a white, sclerosed vessel (*Siegrist spots*).

(d). Large patches of chorioretinal atrophy.

The distinction between vasospastic and *arteriolar sclerotic changes* in the fundus, outlined in detail above, is carried out in the classification suggested by Scheie, given below. The *vasospastic changes* parallel, in general, the clinical severity of the hypertension, whereas the arteriolar sclerotic changes give an indication of the sequential morphological vessel damage associated with prolonged or severe hypertension. The former are more *potentially* reversible than the latter. Scheie's System (choroidal changes are not included):

Vasospastic (hypertensive)	*Grade*	*Arteriolar sclerotic*
Arteriolar narrowing recognizable	I	Recognizable increase in light reflex; minimal A-V compression
Arteriolar narrowing more marked; localized irregularities	II	Increased light reflex, more marked than in Grade I
Accentuation of Grade II findings, accompanied by retinal hemorrhages and/or exudative patches	III	Copper wire arterioles; more marked A-V compression than in Grade II
Findings as under Grade III plus papilledema	IV	Silver wire arterioles; usually striking A-V compression

DIFFERENTIAL DIAGNOSIS

Friedenwald[35, 36] differentiated three other types of retinal vascular abnormalities potentially independent from one another and from the changes due to hypertension which have been described above.

1. *The vascular changes of senescence.* These should be differentiated from pathological, degenerative vascular disease, such as atherosclerosis which may not be inevitable. The fundoscopic picture of senescence is characterized by narrow, straight vessels with diminished light reflexes and a loss of retinal luster. Choroidal changes at the disc, in the macula, and in the periphery are common, being caused by fibrosis and hyalinization of the choroidal capillaries.

2. *Atherosclerosis* causes focal pathology usually not directly visible, having a predilection for the central retinal artery as it passes through the cribiform membrane. If the lumen is partially obstructed, the more peripheral arterial tree is narrowed. Occasionally, the actual atheroma may be observed at the disc, appearing as a local constriction or opaque spot in the vessel wall. If the lumen is occluded, a retinal infarct usually results, characterized by a segmental area of pale coagulation necrosis along the distribution of the occluded vessel. Central arterial thrombosis causes a cherry-red spot in the macula with surrounding pale necrosis. Because of the intimate association of artery and vein, intimal atherosclerosis may invade the vein, causing venous obstruction or thrombosis even though the artery remains patent. Widespread hemorrhagic retinal congestion and edema result. Fibrosis of an atheroma in the retinal artery may cause longitudinal shrinkage of the vessel, straightening the artery and narrowing its angle of bifurcation and/or drawing the retinal branches toward the disc.

3. *Diabetic retinopathy.* Recent studies by Ballantyne and Loewenstein,[4] and by Friedenwald[36] and Ashton[1] have shown that the typical lesion in diabetic retinopathy is the capillary aneurysm, affecting mostly the deeper capillary network, in contrast to the more superficial capillary involvement in hypertension. These microaneurysms appear as "punctate hemorrhages," in contrast to true hemorrhages which though occasionally punctate are usually more flame-shaped. They are almost specific for diabetes. True hemorrhages and waxy exudates may also be seen with diabetes, due to damaged capillaries. The extent of diabetic retinopathy is more clearly correlated with the duration of the disease than with its age of onset, severity, or the nature of its treatment.

PART III. MEDICAL TREATMENT OF HYPERTENSION

On the basis of the evaluations of etiology and prognosis discussed in Parts I and II, one or more of the various forms of therapy of hypertension may be applied. In some cases, treatment of the specific etiologic agent, or such simple measures as reassurance, weight reduction, or mild sedation, may be sufficient. However, in cases of more severe hypertension of unknown or unremediable origin, hypotensive medications may be indicated. Therefore, before presenting a general plan for the management of the various grades of hypertensive disease, it will be helpful to review the properties, side reactions, and clinical use of some of the newer hypotensive drugs. The pharmacological actions of these drugs are summarized in Table C, their clinical preparations and dosages in Table D, and their toxicity and contraindications in Table E.

TABLE C. SUMMARY OF THE PHARMACOLOGICAL ACTIONS OF HYPOTENSIVE AGENTS

R (Raudixin-Reserpine Group); *V* (Veratrum Alkaloids); C_6 (Hexamethonium and Ansolysen); *Ap.* (Apresoline); + indicates a stimulant effect, — a depressant effect on a scale of 0 (absent) to 3 (marked).

	R	*V*	C_6	*Ap.*
CNS	3—	1—	0	2+
Symp. Reflexes	0	0	2—	2+
p-Symp. Reflexes	1+	2+	2—	0
Aortic Reflexes	0	2+	0	0
Epinephrine	0	0	0	0
Renal Circulation	0	0	1—	2+
Water Excretion	1—	1—	3—	2+
Heart Rate	1—	2—	1+	2+
GI Tract and Bladder	1+	3+	3—	1+
Peripheral Vessels	0	0	0	3—

I. THE RAUWOLFIA DRUGS

Rauwolfia Serpentina, one of the 40 or 50 species of Rauwolfia, has been used in India for a long time for anxiety states, hypochondriasis, insomnia, insanity, snake bites, and dysentery.[188] Its mild hypotensive effect was discovered by Indian workers in 1931.[104] Three forms of this drug are in most current use: the crude root (Rauwolfia Serpentina), a purified alkaloid (Reserpine), and an alseroxylon fraction (Rauwiloid). These preparations are only mild hypotensive agents, their widespread use being related to the simplicity and safety of their administration and to their relatively few undesirable or serious side effects.

TABLE D. HYPOTENSIVE DRUGS

Trade name	*Preparation*	*Tablet size (mgm.)*	*Dosage range (mgm.)*	*Duration of action orally*	*Estimated patient cost per day*
Raudixin	Rauwolfia serpentina (Crude powdered root)	50–100	100–1000	1–4 weeks	$.10–$.83
Rau-Sed Serpasil	Resperine (pure alkaloid of Rauwolfia serpentina)	0.1–0.25	0.5–10	1–4 weeks	$.14–$2.00
Rauwoloid Rautensin	Alkaloidal fraction of Rauwolfia serpentina	2	4–16	1–4 weeks	$.20–$.80
	Rauwolfia hetrophilia	100	100–1000		unknown
	Rauwolfia canescens	100	100–1000		unknown
Apresoline	Hydralazine hydrochloride	10–100	100–1000	2–6 hours	$.18–$1.00
Hexameton Methium	Hexamethonium chloride	125–250-500	500–6000	2–6 hours 2–6 hours	$.18–$.90
Ansolysen	Pentapyrrolidium bitartrate (M+B2050)	40–100	120–2200	3–8 hours	$.15–$2.64
	Veratrum Drugs				
Vergitryl	Vergitryl	1 Squibb Unit	3–15 tablets	2–6 hours	$.15–$.75
Vertavis	Vertavis	10 Craw Units	3–12 tablets		$.12–$.48
Veriloid	Veriloid	1–2	8–24		$.36–$.96
Protoveratrine	Protoveratrine	0.5	0.75–6		$.09–$.72

Pharmacological action (see also Table C). The hypotensive, tranquilizing, and sedative properties of the Rauwolfia compounds are thought to be due, at least in large part, to their action at the level of the hypothalamus. Most patients observe a sense of well-being, improved sleep pattern, and decreased excitability and anxiety.

Toxicity and contraindications. The only serious untoward reaction reported so far has been a rare psychosis characterized by severe anxiety and depression. Other toxic effects are listed in Table D. Frequently, these side effects may be eliminated by reduction of dosage or by brief interruption of the drug.

Dosage and clinical use. The effects of Rauwolfia or its derivatives are gradual in onset and cumulative. The hypotensive effect may not become maximal until one to eight weeks after onset of therapy. These preparations are therefore given in daily doses (see Table D) which are reduced when a therapeutic response is obtained.

Fixed, severe, or malignant hypertension seldom responds to Rauwolfia alone. Loeffler[78] treated 51 severe or malignant hypertensives with this drug and observed prolonged reduction in blood pressure in only four patients. Hensler,[58] in treating a group of 60 hypertensives, observed no significant improvement in six cases of nephritis or in three cases of malignant nephrosclerosis. Hypotensive effects of Rauwolfia were observed in only 39% of 218 patients treated by five different groups in America and Europe.[19,25,58,78,88] The Rauwolfia drugs, therefore, cannot be considered as highly effective hypotensive agents in themselves. Nevertheless, they are the drugs of choice in initiating hypotensive treatment, particularly because they often markedly decrease the severity of unpleasant side effects and the total dosage requirements of the more potent agents.

II. VERATRUM COMPOUNDS

Veratrum has been known to possess emetic properties since the early 1800's, its hypotensive effect in eclampsia having been recognized as early as 1860.[84] There was little clinical use of this drug until 1949 at which time various purified extracts (see Table D) were obtained which caused less disagreeable side effects than the crude preparation.

Pharmacological action (see also Table C). The hypotensive effect of veratrum is thought to be mediated through the central nervous system by blockade of carotid and aortic receptors and by peripheral vasodilatation.[98,99,125] The drug has little or no primary sympatholytic or parasympathomimetic activity, and causes only minor changes in renal function.

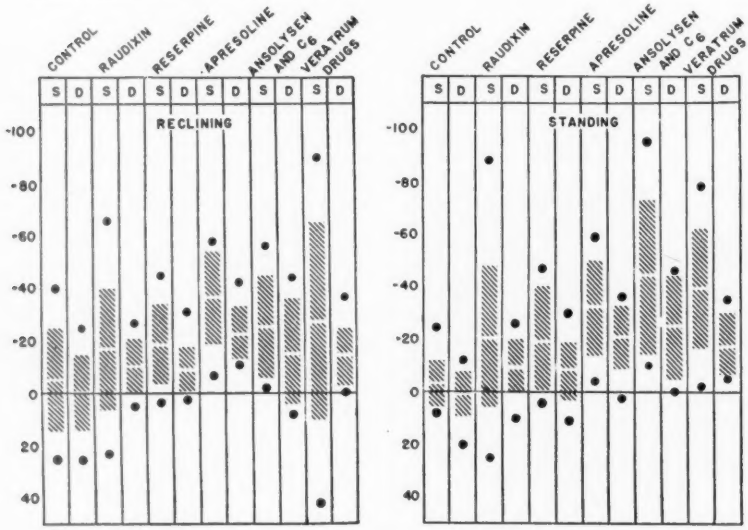
TABLE E. TOXICITY AND CONTRAINDICATIONS OF THE HYPOTENSIVE DRUGS

Drug and chief site of action	*Toxicity*			*Contraindications**
	Serious	*Frequent*	*Infrequent*	
Rauwolfia Cmpds.				
Hypothalamic "tranquilization"	Psychosis	Nasal congestion Bradycardia Sedation Increased appetite	Bronchitis Muscle & joint pains Diarrhea Decreased libido Nightmares	None
Veratrum Cmpds.				
Blockade of carotid and aortic receptors; peripheral vasodilatation	Circulatory collapse	Nausea & vomiting Esophageal burning Increased salivation Bradycardia	Premature contractions Muscle weakness & stiffness Depressed AV conduction Hiccup	Chronic, severe uremia Severe cerebral arteriosclerosis
Apresoline				
Blockade of sympathetic outflow from hypothalamus; Direct peripheral vasodilatation	Increased coronary insufficiency Lupus-like syndrome	Severe headaches Nervousness Nausea & anorexia Diarrhea Malaise Weakness Muscle aches Palpitations	Postural hypotension Fever Numbness & tingling of extremities Dizziness Urticaria Edema Lacrimation Depression & anxiety Aspermia Rheumatoid arthritis Grippe-like state	Chronic uremia Angina pectoris (occ.) Congestive heart failure (occ.)
Hexamethonium and Ansolysen				
Blockade of autonomic ganglia	Cardiovascular collapse Paralytic ileus Interstitial pneumonia Severe renal, cerebral or myocardial ischemia	Orthostatic hypotension Blurred vision Constipation & abdominal cramps Dry mouth Impotence	Anorexia, nausea & vomiting Diarrhea Dizziness Fatigue Nocturia Urinary retention	Severe coronary or cerebral arteriosclerosis Chronic uremia (NPN above 80) Unreliable or unintelligent patient

* Contraindications aside from that of a history of previous severe intoxication from the drug.

Toxicity and contraindications. The margin between the hypotensive effect and the toxic symptoms of veratrum is very small although few, if any, deaths have been attributed directly to the drug. Not infrequently the response to a constant therapeutic dosage varies so much from day to day that nausea and vomiting once or twice a week cannot be avoided. Acquired

DIAGRAM II. CHANGES OF MEAN RECLINING AND STANDING BLOOD PRESSURE (MM. HG). AVERAGE VALUES DURING THE MONTH PRIOR TO TREATMENT COMPARED TO THE AVERAGE VALUES DURING 2-18 MONTHS OF DRUG TREATMENT IN 43 PATIENTS



Legend: Controls indicate variations of blood pressure in the same patients later treated with drugs during periods without specific drug treatment. Hatched blocks indicate standard deviations of changes of systolic (S) and diastolic (D) blood pressure, the clear breaks indicating mean changes of each group, the dots representing the ranges. The changes of reclining blood pressure are significant ($P < .01$) for Apresoline (S & D). The changes of standing blood pressure are significant for Apresoline (S & D), Ansolysen and C_6 (S & D), and the Veratrum drugs (S & D).

tolerance has not been reported. The most frequent side effects, listed in Table E, occur in close relation to therapeutic hypotensive activity. Consequently, the possibility of developing a potent hypotensive extract without unpleasant toxic effects remains remote. Efforts to alleviate these toxic symptoms by the use of atropine, belladonna, thorazine, dramamine, sedation, and Rauwolfia or its derivatives have not been successful. The veratrum preparations are best reserved for moderately severe and malignant

hypertensives (see Diagram II), but are usually ineffective in patients with chronic severe uremia (NPN above 90 mg.%), or with severe cerebral arteriosclerosis.

Dosage and clinical use. The recommended dosage depends upon the specific preparation employed and usually varies from one to five tablets three times daily (see Chart I). Only 9 of 18 patients treated for 2-11 months in this clinic have been able to tolerate continued therapeutic doses of Vergytril or Protoveratrine. Statistically significant blood pressure reduction was observed in all 18 patients (see Diagram II), but toxic symptoms were frequent. Occasionally, left ventricular failure, retinopathy and headaches decreased, electrocardiographic abnormalities became less evident, and gallop rhythm, palpitations and angina subsided.

III. L-HYDRAZINOPHTHALAZINE

Hydralazine compounds characterized by a heterocyclic phthalazine ring and a hydrazine group have been shown to reduce blood pressure in experimental animals[51] and in human subjects.[2, 53, 67, 79, 80, 100, 113] Of all the compounds tested, L-*hydrazinophthalazine* (Apresoline) has had the most extensive clinical trials and has the best effects on blood pressure with the least toxicity.

Pharmacological action (see Table C). The hydralazines react with sulfhydryl radicals, carbonyl radicals, glucose and heavy metals, and are considered antienzymes, inhibiting amine oxidase, histaminase, and DOPA decarboxylase. In therapeutic dosage, they cause little or no peripheral adrenergic blockade (adrenolytic or sympatholytic) but increase cardiac rate and output, and inactivate certain humoral pressor substances such as pherentasin (said to be present in the blood of hypertensives, but not in normal blood).[20] The most powerful hypotensive action has been thought to be via suppression of sympathetic vasopressor impulses from the hypothalamus. However, recent evidence indicates a more important direct peripheral action causing dilatation of constricted vascular smooth muscle. In acute experiments, Apresoline increases renal blood flow, while glomerular filtration is unaffected. However, the renal function of patients with chronic severe renal damage is usually unimproved by the drug.[80]

Toxicity and contraindications. When Apresoline is employed as the sole anti-hypertensive agent, side effects are frequent (see Table E), the most serious being of cardiovascular origin. By augmenting the cardiac output and causing tachycardia, the drug may increase the coronary insufficiency of these patients with pre-existent coronary arteriosclerosis. ST-T segment depressions and T-wave changes closely resembling those of myocardial

anoxia may be observed during the hypotensive response to Apresoline. Acute myocardial infarction has been described within 20 minutes of a dose of the drug.[80] The cardiac effects of the drug may also tend to increase congestive heart failure. Another serious toxic effect is the collagen disorder closely resembling acute lupus erythematosis—even to the finding of typical LE cells in the peripheral blood and bone marrow.[92, 97, 105] Fortunately, this reaction, unlike true lupus, rapidly subsides when Apresoline is discontinued. Severe headaches may be very annoying during initiation of treatment, but usually subside as treatment is continued. Increased nervousness, nausea, and diarrhea are frequent, and, though not serious, may force discontinuance of therapy.

Dosage and clinical use. At the present time it is impossible to select in advance those patients who will respond to Apresoline. It has been suggested that neurogenic hypertension is more likely to respond than the hypertension associated with primary renal disease.[105] The drug is better tolerated if given four times daily (after meals and at bed time). The usual initial dosage of 10 mg. q.i.d. is gradually increased to 50 mg. q.i.d. and then is further increased by increments of 50 mg. per dose until a satisfactory blood pressure response is observed, or until a total daily dose of 800 mg. has been reached. Dosages above 800 mg. usually increase the toxic effects without causing significant further reduction of the blood pressure. Treatment should be continued for at least five weeks before any lack of hypotensive effect is interpreted as a therapeutic failure. If a good response is obtained, the dosage should subsequently be reduced to the least amount consistent with a desired therapeutic or hypotensive effect.

Over a long period, tolerance to the drug commonly develops, as indicated by diminished side effects and less hypotensive response, in spite of gradually increasing dosage.

IV. AUTONOMIC GANGLION BLOCKING AGENTS

In 1950, Smirk reported extensive experimental studies and encouraging clinical results in hypertensives with hexamethonium (C_6). This compound blocks the sympathetic and parasympathetic ganglia causing hypotension by general release of vasoconstrictor tone.[116, 117] In the search for other drugs of similar action with fewer side effects, the bitartrate salt of 1-methylpyrrolidinium was found to have the most satisfactory hypotensive effect. It has had rather extensive clinical trial by Smirk, and by Fries, and is now commercially available under the trade name of Ansolysen.[37, 118, 119]

Pharmacological action (see Table C). Therapeutic dosage of either hexamethonium or Ansolysen causes the following:

1. Fall in systemic and pulmonary blood pressures
2. Drop in peripheral resistance
3. Increase in blood flow and skin temperature of the extremities
4. Inhibition of gastric and salivary gland secretions
5. Disturbance of eye accommodation
6. Decrease in renal blood flow.

The hypotensive effects are most pronounced when the patient is upright, and are quite minimal when the patient is supine.

Toxicity and contraindications. Toxic effects of Ansolysen are similar to those of C_6 (see Table E), although less severe, probably because the dosage of Ansolysen is more easily controlled (see below). Cholinergic drugs such as pilocarpine nitrate and urecholine are of slight value in controlling side effects—particularly those related to the urinary, gastrointestinal, and visual systems. Reading glasses may be necessary to relieve blurring of vision in patients whose professions or occupations require clear vision. Because of pupillary paralysis, tinted glasses may be necessary during exposure to sunlight. Important contraindications to both drugs are listed in Table E. In general, these contraindications are more absolute for C_6 than for Ansolysen.

Dosages and clinical use.

A. *Hexamethonium (C_6) chloride.* Oral dosage of C_6 is difficult to regulate because of incomplete and variable intestinal absorption of the drug and because of the rapid development of drug tolerance. Changes of environmental temperature, physical activity, and daily meals, or the consumption of alcohol, tend to cause marked fluctuations in the hypotensive response to a constant daily oral dose. It is therefore advisable, where possible, to begin treatment while the patient is under close observation in the hospital (not at bed rest), and to instruct the patient or a member of his family in the technique of measuring his blood pressure. Ambulatory treatment may be started by administering 125 mg. q.i.d. (expressed in terms of hexamethonium chloride). The dose is increased to 250 mg. q.i.d. during the first week, and thereafter by weekly increments of 250 mg./dose until an adequate hypotensive response (as indicated by the *standing* blood pressure) is obtained, or until distressing side effects force discontinuance of the drug. The therapeutic aim should be to reduce the blood pressure toward normal, while avoiding symptomatic or prolonged hypotension.

Parenteral dosage of C_6 is somewhat more reliable in its effects than oral dosage for reasons indicated above. Although the drug may be administered intravenously in hypertensive emergencies, it is better given subcutaneously

about every 8 hours, particularly where continued parenteral treatment is contemplated. Maintenance therapy can be continued indefinitely at home by proper instruction of the patient (or a relative) in the technique of

TABLE F. RECOMMENDED MEDICAL THERAPY OF HYPERTENSION

Severity of disease	*Initial treatment*	*Supplementary treatment*
(1) Mild labile hypertension with diastolic pressures between 100 and 110 mm. Hg (Grade I) (Smithwick)	Weight reduction Reduce responsibilities Phenobarbital	Rauwolfia serpentina or derivatives Selective psychotherapy
(2) Fixed mild hypertension with diastolic pressures between 100 and 120 mm. Hg (Grade II) (Smithwick)	Rauwolfia serpentina or derivatives	Low Na diets, Veratum drugs or Apresoline
(3) Fixed moderately severe hypertension with diastolic pressures above 120 mm. Hg—not malignant (Grade III) (Smithwick)	Rauwolfia serpentina or derivatives Veratrum drugs or Apresoline	Hexamethonium chloride or Ansolysen 200 mgm. Na diet (or rice diet)
(4) Malignant hypertension (Grade IV) (Smithwick)	200 mgm. Na diet (or rice diet) Combination of Apresoline with hexamethonium or Ansolysen	Intramuscular drug therapy (C_6 or Ansolysen)
(5) Hypertension with renal failure (NPN>50)	200 mg. Na diet (or rice diet), if no salt-wasting. Veratrum drugs (NPN<90)	Apresoline not recommended Ansolysen and C_6 to be used with great caution
(6) Hypertensive emergencies	Intravenous drug therapy (Veratrum drugs, hexamethonium or Ansolysen)	

sterile injection, and in the regulation of dosage according to frequent measurements of the standing blood pressure. Parenteral therapy is best begun with a 2 mg. dose (expressed in terms of the hexamethonium ion), the patient being kept in a semi-sitting position in order to determine the degree of orthostatic hypotensive effect. Each dose is then increased 5 to 10 mg. at 6-8 hour intervals until optimal and stable hypotensive effects are attained. Any profound fall in blood pressure should be counteracted by

immediate postural readjustment (to the supine or head-down position), or by using vasoconstrictor drugs (e.g., methoxamine hydrochloride, or arterenol by infusion).

B. *Ansolysen.* During recent years, this drug has largely supplanted hexamethonium chloride, particularly in the treatment of moderately severe and malignant hypertension,[27, 119] because of its more complete and constant absorption from the intestines, and because of its allegedly more prolonged action.[7] As compared with hexamethonium (on the basis of parenteral

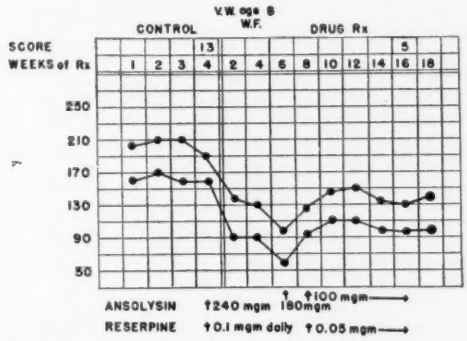


FIG. 1. Female patient with severe hypertension associated with polycystic kidneys and following poliomyelitis. Blood pressure responded well, and "score" (by the method of Table A) changed from 13 to 5.

administration), it is thought to be 2-4 times more active on the sympathetic, and 1-2 times more active on the parasympathetic nervous systems. Oral administration may be safely begun in ambulatory patients with doses of 20-40 mg., a.c., q.i.d., and then increased by daily increments of 10-20 mg./dose until the desired hypotensive effects are obtained. Precautions similar to, but less strict than, those outlined for hexamethonium are advisable.

Parenteral administration is unnecessary for maintenance therapy but may be indicated for hypertensive emergencies. In such cases, the drug is given intravenously or subcutaneously in the same way as has been described above for C_6, but in smaller doses, careful control of the semi-sitting blood pressure being required. The dosage is increased at 6-8 hour intervals in increments of 2 mg./dose, after an initial dose of 2 mg. Because of the potential hazards of any autonomic blocking agent, Ansolysen—even though more easily administered than hexamethonium—should also be reserved for patients with severe hypertension (see Table F).

V. THE USE OF THE HYPOTENSIVE DRUGS UNDER SPECIAL CIRCUMSTANCES

A. *Hypertension in pregnancy.* Toxemia of pregnancy may be defined as a disease characterized by hypertension, edema, and albuminuria which is peculiar to pregnancy, usually occurring during the third trimester (see Part I). Since its pathological physiology involves widespread arteriolar vasoconstriction and decreased blood flow to major organs such as the kidneys, uterus, and brain, therapy logically includes measures directed toward arteriolar dilatation. The ordinary sedatives are useful in this

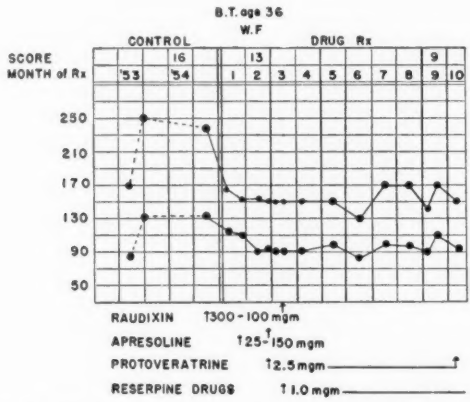


FIG. 2. Female patient with severe essential hypertension. Blood pressure reduced, papilledema reversed, and score changed from 16 to 9 with a succession of medications. Apresoline had to be stopped because of severe nasal stuffiness and anxiety state.

regard, and intravenously administered magnesium sulfate (which has sedative as well as hypotensive actions) is useful in "pre-eclampsia" or "eclampsia." However, it seems logical to attempt to alleviate toxemic hypertension and its related symptoms with more purely hypotensive agents, in order to avoid deleterious depressant effects of oversedation on the infant, and in order to allow adequate clinical observation for other untoward (particularly cerebral) symptoms. For this purpose, the usefulness of the *Veratrum compounds* has been indicated in extensive clinical trials in which mortality from toxemia seems to have been reduced.[9, 32] *Apresoline,* which lowers the blood pressure and increases renal functions, cerebral blood flow, and cardiac output in toxemia,[2] also appears to be a suitable agent for the treatment of this disease. The *ganglionic blocking agents* effectively reduce toxemic hypertension, but have the disadvantage of impairing renal flow and glomerular filtration, and cerebral blood flow. They have

been used, therefore, chiefly in cases of toxemia superimposed on essential hypertension.

B. *Hypertensive crises.* Acute hypertensive crises, such as *encephalopathy* or *acute pulmonary edema* may be managed by cautious use of intravenous Veratrum or ganglionic blocking agents, administered in graded doses well diluted in a suitable vehicle such as saline or 5% glucose (see the discussions of each drug for further details). As indicated previously, lowering of the blood pressure in this way is more likely to relieve

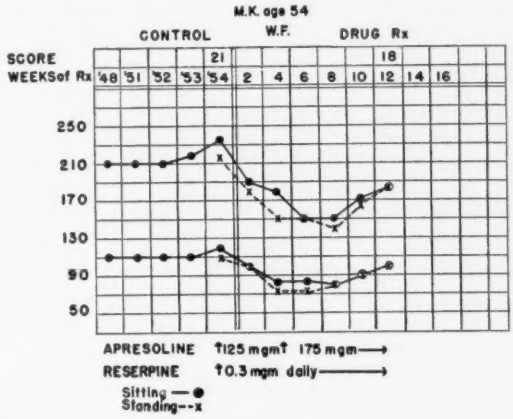


FIG. 3. Female patient in the incipient phase of malignant hypertension, with a recent cerebral vascular accident, whose blood pressure responded well and whose score changed only from 21 to 18 in three months of therapy.

acute pulmonary edema, which usually tends to be functionally reversible, than to relieve *encephalopathy,* which is often the concomitant of fulminant vascular disease and/or uremia.

VI. THE USE OF THE HYPOTENSIVE DRUGS IN CONJUNCTION WITH LOW SODIUM DIETS

The impressive work of Kempner has prompted extensive interest in the use of low sodium diets in the treatment of hypertension.[89] The effectiveness (30-50%) of the various low sodium diets has been confirmed, but few patients in their normal environments are able to tolerate the stringent deprivations which are required. The critical level of sodium intake for adequate treatment of hypertension is about 200 mg. of sodium per day. Diets which contain more than this quantity of sodium are probably ineffective in the management of essential or malignant hypertension except in controlling

congestive heart failure. Serious complications such as the development of the low sodium syndrome, renal failure, or severe metabolic acidosis, are unusual except in patients with marked renal impairment. However, side effects such as weight loss, weakness, and mental depression are frequent.

In spite of the above disadvantages, the low sodium diet may be very useful in selected cases to potentiate the effects of the autonomic blocking agents if the latter have been partially or even completely ineffective.

VII. AN OVER-ALL PLAN FOR THE MEDICAL MANAGEMENT OF VARIOUS GRADES OF HYPERTENSION

In the previous sections, the actions and uses of individual drugs have been discussed. In practice, it is usually desirable to combine one or more drugs with more general supportive measures in order to take advantage of complimentary hypotensive effects, while avoiding the side effects associated with the larger doses of each preparation. Table F suggests, in outline, a plan for such combined therapy. Representative cases illustrating successful results of combined drug therapy are illustrated in Figures 1-3. The average responses of blood pressure to various drugs in 56 patients are given in Diagram II. Seventy per cent of these patients had "essential hypertension." Thirteen per cent had malignant hypertension (scores of 21 or more, according to criteria of Table A), 40% had severe hypertension (scores 14-20), 36% had moderate hypertension (scores 8-13), and 91% had mild hypertension (scores 1-7).

It would seem from our experience summarized in Diagram II that Apresoline, Veratrum, and the autonomic blocking agents have been useful in lowering the standing blood pressure of many patients. However, the ultimate long-term value of the use of such drugs, particularly with respect to the reversal or interruption of the course of organic vascular disease, remains to be proven.

REFERENCES

1 Ashton, N.: Vascular changes in diabetes with particular reference to retinal vessels. Brit. J. Ophth., 1949, *33*, 407.
2 Assali, N. S.: Studies on Veratrum viride: Standardization of intravenous technique and its clinical application in treatment of toxemia of pregnancy. Am. J. Obst., 1950, *60*, 387.
3 Assali, N. S. and Suyemoto, R.: The place of hydrazinophthalazine and thiophanium compounds in the management of hypertensive complications of pregnancy. Am. J. Obst., 1952, *64*, 1021.
4 Ballantyne, A. J. and Loewenstein, A.: Retinal micro-aneurysms and punctate hemorrhages. Brit. J. Ophth., 1944, *28*, 593.
5 Bechgaard, P.: Arterial hypertension: A follow-up study of 1,000 hypertonics. Acta med. scand., 1946, Supp. 172, p. 3.

6 Binger, C. A. L., Ackerman, N. W., Cohn, A. E., Schroeder, H. A., and Steele, J. M.: *Personality in arterial hypertension.* New York, Psychosomatic Med. Monographs, 1945.

7 Birkhead, N. C. and Allen, E. V.: Comparison of effects on hypertension of hexamethonium and pentapyrrolidinium injected subcutaneously. Proc. Mayo Clin., 1954, *29,* 489.

8 Bordley, J., Caenor, C. A. R., Hamilton, W. F., Ken, W. J., and Wiggers, C. J.: Recommendations for human blood pressure determinations by sphygmomanometers. Circulation, 1951, *4,* 503.

9 Bradley, S. E.: Physiology of essential hypertension. Am. J. Med., 1948, *4,* 398.

10 Bradley, S. E., Bradley, G. P., Tyson, C. J., Curry, J. J., and Blake, W. D.: Renal function in renal diseases. Am. J. Med., 1950, *9,* 766.

11 Brust, A. A., Reiser, M. F., and Ferris, E. B., Jr.: Evaluation of neurogenic control of blood pressure in hypertension with TEAC and spinal anesthesia. J. Clin. Invest., 1951, *30,* 925.

12 Burch, G. E., Cohn, A. E., and Neuman, C.: Reactivity of intact blood vessels of the fingers and toes to sensory stimuli in normal resting adults, in patients with hypertension, and in senile subjects. J. Clin. Invest., 1942, *21,* 655.

13 Byrom, F. B.: The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension; experimental evidence from the hypertensive rat. Lancet, Lond., 1954, *267,* 201.

14 Cahill, G. F.: Pheochromocytoma. Bull. N. York Acad. M., 1953, *29,* 749.

15 Castlemen, B. and Smithwick, R. H.: The relation of vascular disease to the hypertensive state. New England J. M., 1948, *239,* 732.

16 Chapman, W. P. and Singh, M.: Evaluation of tests used in the diagnosis of pheochromocytoma. Mod. Concepts Card. Dis., 1954, April.

17 Collins, B. A. and Wood, E. H.: Experimental renal hypertension and adrenalectomy. Am. J. Physiol., 1938, *123,* 224.

18 Corcoran, A. C., Page, I. H., Masson, G. M. C., Taylor, R. D., and Dustan, H.: Hypertension and hypertensive cardiovascular disease. Arch. Int. M., 1951, *87,* 732.

19 Damm, G. and Trauter, H.: On the treatment of hypertension with reserpine (Serpasil). Deut. med. Wschr., 1954, *79,* 39.

20 Davies, D. F., Olsen, N. S., and Schroeder, H. A.: Pressor substances in arterial hypertension. Circulation, 1952, *5,* 380.

21 Dexter, L. and Weiss, S.: *Toxemia of pregnancy.* New York, Little, Brown & Co., 1951.

22 Doyle, A. E. and Smirk, F. H.: The use of pure Veratrum alkaloids, neogermitrine and protoveratrine in hypertension. Brit. Heart J., 1953, *15,* 439.

23 Duke-Elder, W. S.: *Textbook of ophthalmology,* Vol. III. New York, C. V. Mosby Co., 1941.

24 Dwyer, H. L., Jr.: Normal blood pressure. Conn. State M. J., 1951, *15,* 693.

25 Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H.: Clinical experiences with reserpine (Serpasil). A controlled study. Reported at the meeting of the New York Academy of Sciences, Feb. 5, 1954.

26 Earle, D. P., Jr.: Renal function tests in the diagnosis of glomerular and tubular disease. Bull. N. York Acad. M., 1950, *26,* 47.

27 Ehrlich, A., Brodoff, B. N., Rubin, I. L., and Berkman, J. I.: Malignant hypertension in a patient with renal artery occlusion. Arch. Int. M., 1953, *92,* 591.

28 Evans, J. A., Rubitsky, H. J., Bartels, C. C., and Bartels, E. C.: Re-evaluation of the reliability of pharmacologic and cold pressor studies in hypertension and pheochromocytoma. Am. J. Med., 1951, *11,* 448.

29 Frant, R. and Groen, J.: Prognosis of vascular hypertension. Arch. Int. M., 1950, *85,* 727.

30 Fertig, H. H., Taylor, R. D., Corcoran, A. C., and Page, I. H.: The renal manifestations of pheochromocytomata: Report of a case. Ann. Int. M., 1951, *35,* 1358.

31 Findley, T.: Role of the neurohypophysis in the pathogenesis of hypertension and some allied disorders associated with aging. Am. J. Med., 1949, *7,* 70.

32 Finnerty, F. A.: Hypertensive toxemias of pregnancy. N. England J. M., 1952, *246*, 646.

33 Finnerty, F. A. and Fuchs, J. S.: The veratrum treatment of toxemia of pregnancy. Proc. Am. Heart Ass., 1953, 26th Scientific Session.

34 Finnerty, F. A.: Does vascular damage follow toxemia of pregnancy? J. Am. M. Ass., 1954, *154*, 1075.

35 Friedenwald, J. S.: Disease processes versus disease pictures in interpretation of retinal vascular lesions. Arch. Ophth., 1947, *37*, 403.

36 Friedenwald, J. S.: *Ophthalmic pathology:* an atlas and textbook. Philadelphia, W. B. Saunders Company, 1952.

37 Fries, E. D., Partenope, E. A., Lilienfield, L. S., and Rose, J. C.: A clinical appraisal of pentapyrrolidinium (M & B 2050) in hypertensive patients. Circulation, 1954, *9*, 540.

38 Gifford, R. W., Jr., Roth, G. M., and Kvale, W. F.: Evaluation of new adrenolytic drug (regitine) as test for pheochromocytoma. J. Am. M. Ass., 1952, *149*, 1628.

39 Goodman, H. L.: Malignant hypertension with unilateral renal-artery occlusion. N. England J. M., 1952, *246*, 8.

40 Goldblatt, H.: Studies in experimental hypertension. V. The pathogenesis of experimental hypertension due to renal ischemia. Arch. Int. M., 1937, *11*, 69.

41 Goldenberg, M., Aranow, H., Jr., Smith, A. A., and Faber, M.: Pheochromocytomata and essential hypertensive vascular disease. Arch. Int. M., 1950, *86*, 823.

42 Goldenberg, M.: Adrenal medullary function. Am. J. Med., 1951, *10*, 627.

43 Goldenberg, M., Serlin, I., Edwards, T., and Rapport, M. M.: Chemical screening methods for the diagnosis of pheochromocytoma. I. Norepinephrine and epinephrine in human urine. Am. J. Med., 1954, *16*, 310.

44 Golding, W.: Clinical application of current tests of renal function. J. Am. M. Ass., 1953, *153*, 1245.

45 Goldman, M. L. and Schroeder, H. A.: Immediate pressor effect of desoxycorticosterone acetate in arterial hypertension. Am. J. Med., 1948, *5*, 33.

46 Graham, G. K., Taylor, J. A., Ellis, L. B., Greenberg, D. J., and Robbins, S. L.: Studies in mitral stenosis. Arch. Int. M., 1951, *88*, 532.

47 Graybiel, A., Allen, A. W., and White, P. D.: A histologic study of the arterioles of the muscle and skin from the arm and leg in individuals with coarctation of the aorta. J. Clin. Invest., 1935, *14*, 52.

48 Gressel, G. C., Shobe, F. O., Saslow, G., DuBois, P. H., and Schroeder, H. A.: Personality factors in arterial hypertension. J. Am. M. Ass., 1949, *140*, 3.

49 Griep, H. H., Barry, G. R., Hall, W. C., and Hoobler, S. W.: The prognosis in arterial hypertension. Am. J. M. Sc., 1951, *221*, 239.

50 Grimson, K. S., Orgain, E. S., Anderson, B., Broane, R. A., Jr., and Longino, F. H.: Caution with regard to use of hexamethonium and "apresoline." Ann. Surg., 1949, *129*, 850.

51 Gross, F., Druey, J., and Meier, R.: Eiene neue Gruppe bluddrucksenkender Substanzen von besonderem Wirkungscharakter. Experientia, Basel, 1950, *6*, 19.

52 Gross, R. E.: Coarctation of the aorta. Circulation, 1950, *1*, 41.

53 Hafkenschiel, J. H. and Lendauer, M. A.: 1-Hydrazinophthalazine (Apresoline) in the treatment of hypertension: A two-year study. Circulation, 1953, *7*, 52.

54 Hamilton, M., Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C.: The etiology of essential hypertension. I. The arterial pressure in the general population. Clin. Sc., Lond., 1954, *13*, 11.

55 Hammerstrom, S. and Bechgaard, P.: Prognosis in arterial hypertension: A comparison between 251 patients after sympathectomy and a selected series of 435 non-operated patients. Am. J. Med., 1950, *8*, 53.

56 Handler, P. and Bernheim, F.: Effect of choline deficiency on ACTH production and on hypertension of subtotally nephrectomized rats. Am. J. Physiol., 1950, *162*, 375.

57 Hatch, F. T., Wertheim, A. R., Eurman, G. H., Watkins, D. M., Froeb, H. F., and Epstein, H. A.: Effects of diet in essential hypertension. Am. J. Med., 1954, *17*, 499.

58 Hensler, L.: Treatment of hypertension with Serpasil, a Rauwolfia Serpentina alkaloid. Schweiz. med. Wschr., 1953, *83*, 1162.

59 Hepaistall, R. H.: Renal biopsies in hypertension. Brit. Heart J., 1954, *16*, 133.

60 Heymans, C. and van den Heuval-Heymans, G.: New aspects of blood pressure regulation. Circulation, 1951, *4*, 581.

61 Hilker, R. R. J., Rhoads, P. S., and Billings, C. E.: Clinical use of hydralazine and hexamethonium in treatment of hypertension. J. Am. M. Ass., 1953, *153*, 1.

62 Hines, E. A. and Brown, G. E.: A standard test for measuring the variability of blood pressure: its significance as an index of the pre-hypertensive state. Ann. Int. M., 1933, *7*, 209.

63 Hines, E. A.: Range of normal blood pressure and subsequent development of hypertension. J. Am. M. Ass., 1940, *115*, 271.

64 Howard, J. E., Berthrong, M., Sloan, R. D., and Yendt, E. R.: Relief of malignant hypertension by nephrectomy in four patients with unilateral renal vascular disease. Tr. Ass. Am. Physicians, 1953, *56*, 164.

65 Jeffers, W. A., Zintel, H. A., Hafkenschiel, J. H., Hills, A. G., and Sellers, A. M.: Evaluation of adrenal resection and sympathectomy in 99 persons with hypertension. J. Am. M. Ass., 1953, *153*, 1502.

66 Jeffers, W. A., Zintel, H. A., Hills, A. G., Hafkenschiel, J. H., Langfeld, S. B., Sellers, A. M., and Wolferth, C. C.: Further observations on patients with severe hypertension subjected to adrenal resection and sympathectomy. Ann. Int. M., 1954, *41*, 221.

67 Johnson, R. L., Freis, E. D., and Schnaper, H. W.: Clinical evaluation of L-Hydrazinophthalazine (C5968) in hypertension. Circulation, 1952, *5*, 833.

68 Keith, N. M., Wagener, H. P., and Barker, N. W.: Some different types of essential hypertension: Their course and prognosis. Am. J. M. Sc., 1939, *197*, 332.

69 Kempner, W.: Treatment of hypertensive vascular disease with rice diet. Am. J. Med., 1948, *4*, 545.

70 Kerschner, C. M.: *Blood supply of the visual pathway*. Boston, Meador Publishing Co., 1943.

71 Kezdi, P.: Sinoaortic regulatory system. Arch. Int. M., 1953, *91*, 26.

72 Livesay, W. R., Moyer, J. H., and Miller, S. I.: Treatment of hypertension with Rauwolfia Serpentina alone and combined with other drugs. J. Am. M. Ass., 1954, *155*, 1027.

73 Loeffler, W., Esselier, A. F., Prott, F., and Wegman, A.: Treatment of hypertension with Rauwolfia alkaloid (Serpasil). Schweiz. med. Wschr., 1953, *83*, 1012.

74 Master, A. M., Dublin, L. I., and Marks, H. H.: The normal blood pressure range and its clinical implications. J. Am. M. Ass., 1950, *143*, 1464.

75 Master, A. M., Goldstein, I., and Walters, M. B.: New and old definition of normal blood pressure: clinical significance of newly established limits. Bull. N. York Acad. M., 1951, *27*, 452.

76 Merrill, J. P.: The role of the adrenal in hypertension. Ann. Int. M., 1952, *37*, 966.

77 Michaelson, I. C.: *Retinal circulation in man and animals*. Springfield, Charles C Thomas, 1954.

78 Morrow, J. D., Schroeder, H. A., and Perry, H. M., Jr.: Studies on the control of hypertension by hyphex. II. Toxic reactions and side effects. Circulation, 1953, *8*, 829.

79 Moyer, J. H., Handley, C. A., and Huggins, R. A.: Some pharmacodynamic effects of L-hydrazinophthalazine (C5968) with particular reference to renal function and cardiovascular response. J. Pharm. Exp. Ther., 1951, *103*, 368.

80 Moyer, J. H.: Hydrallazine (Apresoline) hydrochloride. Arch. Int. M., 1953, *91*, 419.

81 Moyer, J. H., Miller, S. I., and Ford, R. V.: Orally administered hexamethonium chloride in hypertension. J. Am. M. Ass., 1953, *152*, 1121.

82 Moyer, J. H., Miller, S. I., Tashnek, A. B., Snyder, H., and Bowman, R. O.: Malignant hypertension and hypertensive encephalopathy. Am. J. Med., 1953, *14*, 175.

83 Moyer, J. H.: Observations on the cardiovascular and renal hemodynamic response to reserpine (Serpasil) and clinical results in the treatment of hypertension. Reported at the meeting of the New York Academy of Sciences, Feb. 5, 1955.

84 Osgood, C.: Observations on the medicinal properties of the Veratrum Viride. Am. J. M. Sc., 1835, *16*, 296.

85 Palmer, R. S., Loofbourow, D., and Doering, C. R.: Prognosis in essential hypertension: An eight-year follow-up study of 430 patients on conventional medical treatment. N. England J. M., 1948, *239*, 990.

86 Page, I. H.: Treatment of essential and malignant hypertension. J. Am. M. Ass., 1951, *147*, 1311.

87 Perera, G. A.: Diagnosis and natural history of hypertensive vascular disease. Am. J. Med., 1948, *4*, 416.

88 Perera, G. A.: The adrenal cortex and hypertension. Bull. N. York Acad. M., 1950, *26*, 75.

89 Perera, G. A.: Cortisone and blood pressure. Proc. Soc. Exp. Biol., N. Y., 1951, *76*, 583.

90 Perera, G. A. and Haelig, A. W.: Clinical characteristics of hypertension associated with unilateral renal disease. Circulation, 1952, *6*, 549.

91 Perera, G. A.: Development of hypertensive manifestations after the disappearance of hypertension. Circulation, 1954, *10*, 28.

92 Perry, H. M. and Schroeder, H. A.: Syndrome simulating collagen disease caused by hydralazine (Apresoline). J. Am. M. Ass., 1954, *154*, 670.

93 Pickering, G. W.: The peripheral resistance in persistent arterial hypertension. Clin. Sc., Lond., 1936, *2*, 209.

94 Rall, J. E.: Congenital polycystic disease of the kidney: review of the literature and data on 207 cases. Am. J. M. Sc., 1949, *218*, 399.

95 Rassmussen, H. and Boe, J.: Prognosis of essential hypertension with remarks respecting indications for operative treatment. Acta med. scand., 1945, *120*, 12.

96 Ratliff, R. K., Mesbit, R. M., Plumb, R. T., and Bohne, W.: Nephrectomy for hypertension with unilateral renal disease. J. Am. M. Ass., 1947, *133*, 296.

97 Reinhardt, D. J. and Waldron, J. M.: Lupus erythematosus-like syndrome complicating hydralazine (Apresoline) therapy. J. Am. M. Ass., 1954, *155*, 1491.

98 Richardson, A. P., Farrar, C., and Walker, H. A.: Effect of Veratrum alkaloids on the carotid sinus pressor reflex. Exp. Therapy, 1951, *103*, 74.

99 Richardson, A. P., Walker, H. A., Farrar, C. B., Griffith, W., Pound, E., and Davidson, J. R.: Mechanism of hypotensive action of veratrine alkaloids. Proc. Soc. Exp. Biol., N. Y., 1952, *79*, 79.

100 Rivin, S. S., Pocock, D. G., Kory, R. C., Roehm, D. C., Anderson, R. S., and Meneely, G. R.: The control of hypertension with L-hydrazinophthalazine (Apresoline). Am. J. Med., 1953, *14*, 160.

101 Roberts, L. N., Smiley, J. R., and Manning, C. W.: A comparison of direct and indirect blood pressure determinations. Circulation, 1953, *8*, 232.

102 Robinson, S. C. and Brucer, M.: Range of normal blood pressure: Statistical and clinical study of 11,383 persons. Arch. Int. M., 1939, *64*, 409.

103 Selye, H.: Production of hypertension and hyalinosis by desoxycorticosterone. Brit. M. J., 1950, *1*, 203.

104 Sen, G. and Bose, K. C.: *Rauwolfia Serpentina*, a new Indian drug for insanity and high blood pressure. Ind. M. World, 1931, *2*, 194.

105 Shackman, N. H., Swiller, A. I., and Morrison, M.: Syndrome simulating acute disseminated lupus erythematosus. J. Am. M. Ass., 1954, *155*, 1492.

106 Schaffer, A. J. and Markowitz, M.: Hypertension treated by nephrectomy: a report of 4 additional cases and a re-evaluation of prognosis and criteria for operation. Am. J. M. Sc., 1954, *227*, 417.
107 Scheie, H. S.: Evaluation of ophthalmoscopic changes of hypertension and arteriolar sclerosis. Arch. Ophth., Chic., 1953, *49*, 1.
108 Schottstaedt, M. F. and Sokolow, M.: Natural history and course of hypertension with papilledema (malignant hypertension). Am. Heart J., 1953, *45*, 331.
109 Schroeder, H. A., Davies, D. F., and Clark, H. E.: A syndrome of hypertension, obesity, menstrual irregularities and evidence of adrenal cortical hyperfunction. J. Laborat. Clin. M., 1949, *34*, 1746.
110 Schroeder, H. A., Futcher, P. H., and Goldman, M. L.: The effects of the "rice diet" upon the blood pressure of hypertensive individuals. Ann. Int. M., 1949, *30*, 713.
111 Schroeder, H. A. and Olsen, N. S.: Pherentasin: a pressor substance present in arterial hypertension. J. Clin. Invest., 1950, *29*, 844.
112 Schroeder, H. A.: Pathogenesis of hypertension. Am. J. Med., 1951, *10*, 189.
113 Schroeder, H. A.: The effect of L-hydrazinophthalazine in hypertension. Circulation, 1952, *5*, 28.
114 Schroeder, H. A., Morrow, J. D., and Perry, H. M., Jr.: Studies of the control of hypertension by Hyphex. I. Effects on blood pressure. Circulation, 1953, *8*, 672.
115 Schroeder, H. A., Morrow, J. D., and Perry, H. M., Jr.: Studies of the control of hypertension by Hyphex. V. Effects on the course of the malignant stage. Circulation, 1954, *10*, 321.
116 Smirk, F. H.: Methonium compounds in hypertension. Lancet, Lond., 1950, *2*, 477.
117 Smirk, F. H.: Practical details of the methonium treatment of high blood pressure. N. Zealand M. J., 1950, *49*, 637.
118 Smirk, F. H.: Action of a new methonium compound in arterial hypertension. Pentamethylene 1:5 bis N (N methyl-pyrrolodinium bitartrate (M & B 205A). Lancet, Lond., 1953, *1*, 457.
119 Smirk, F. H.: Practical details of the treatment of hypertension by hexamethonium salts and by pentamethylene 1:5 bis N (N methyl-pyrrolidinium) bitartrate (M & B 2050A). N. Zealand M. J., 1953, *52*, 325.
120 Smirk, F. H.: The management of hypertension with special reference to the methonium compounds. American College of Physicians Television Symposium, Sept., 1954.
121 Smith, H. W.: Hypertension and urologic disease. Am. J. Med., 1948, *4*, 724.
122 Smithwick, R. H.: An evaluation of the surgical treatment of hypertension. Bull. N. York Acad. M., 1949, *25*, 698.
123 Sorsby, A.: *Systemic ophthalmology*. London, Butterworth, 1951.
124 Stunkard, A. J., Eurman, G. H., Wachpress, M., and Wertheim, A. R.: Treatment of hypertensive disease with hydralazine. Am. J. Med., 1954, *17*, 712.
125 Taylor, R. D. and Page, I. H.: Further studies of the cerebral chemoreceptor buffers as influenced by vasoconstrictor and vasodilator drugs and Veratrum viride. Circulation, 1951, *4*, 184.
126 Taylor, R. D., Dustan, H. P., Corcoran, A. C., and Page, I. H.: Evaluation of L-hydrazinophthalazine (Apresoline) in treatment of hypertensive disease. Arch. Int. M., 1952, *90*, 734.
127 Taylor, R. D., Corcoran, A. C., and Page, I. H.: Increased cerebrospinal fluid pressure and papilledema in malignant hypertension. Arch. Int. M., 1954, *93*, 818.
128 Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Jr., Roche, M., Staehlin, D., and Wilson, D. L.: The clinical usefulness of ACTH and cortisone. N. England J. M., 1950, *242*, 783.
129 Thorpe, J. J., Welch, W. J., and Poindexter, C. A.: Bilateral thoracolumbar sympathectomy for hypertension. A study of 500 cases. Am. J. Med., 1950, *9*, 500.

130 Van Bergen, F. H., Weatherhead, D. S., Treloar, A. E., Dobkin, A. B., and Buckley, J. J.: Comparison of indirect and direct methods of measuring arterial blood pressure. Circulation, 1954, *10*, 481.
131 Von Euler, U. S. and Liljistrand, G.: The regularity of the blood pressure with special reference to muscular work. Acta physiol. scand., 1946, *12*, 279.
132 Wagener, H. P., Clay, S. E., and Gipner, F. F.: Classification of retinal lesions in the presence of vascular hypertension. Tr. Am. Ophth. Soc., 1947, *45*, 57.
133 Wallis, T. E. and Rohatgi, S.: The pharmacognosy of Rauwolfia. J. Pharm. Pharmacol., 1949, *1*, 292.
134 Waters, L. L.: Changes in coronary arteries of dog following injection of allylamine. Am. Heart J., 1948, *35*, 212.
135 Waters, L. L. and de Suto-Nagy, G. I.: Circulatory factors in the pathogenesis of experimental arteriolar necrosis. Yale J. Biol., 1950, *22*, 751.
136 Watkin, D. M., Froeb, H. F., Hatch, F. T., and Gutman, A. B.: Effects of diet in essential hypertension. Am. J. Med., 1950, *9*, 428.
137 Weiss, E .:Psychosomatic aspects of hypertension. J. Am. M. Ass., 1942, *120*, 1081.
138 Whitelaw, G. P. and Smithwick, R. H.: The effect of extensive sympathectomy upon blood pressure responses and levels. Angiology, 1951, *2*, 157.
139 Zweifach, B. W. and Shorr, E.: *Hepatorenal vasotropic factors in blood of patients with essential hypertension.* Conference on Factors Regulating Blood Pressure. New York, Josiah Macy, Jr. Foundation, 1948.
140 Zweifach, B. W., Shorr, E., Baez, S., and Rosenfeld, S.: Hepatorenal factors in circulatory hemostasis; relation of adrenals to formation of a renal vaso-excitor principle. J. Clin. Endocr., 1949, *7*, 460.

Articles are accepted for publication in *The Yale Journal of Biology and Medicine* on the basis of merit and suitability. The privilege of submitting articles is not limited to those associated with Yale University and contributions from others are cordially invited.

The Board of Editors

EVENTS

PHYSIOLOGY SEMINAR

April 5, 1955

THE FUNCTION OF THE PITUITARY STALK IN RELATION TO THE SECRETION OF ACTH. By G. W. Harris, Department of Neuroendocrinology, Institute of Psychiatry, Maudsley Hospital, London, England.

Certain exteroceptive stimulation is followed by alterations in the release of several adenohypophysial hormones. The central nervous system (especially the hypothalamus) is thus implicated as a link between the *milieu extérieur* and the adenohypophysis. Although a direct neural connection between the hypothalamus and the adenohypophysis has not been demonstrated, the hypophysial portal system provides a vascular connection. Blood flows in this portal system through the median eminence and infundibulum before reaching the adenohypophysis. To some investigators such a vascular connection suggests the transport of a neurohumor from the hypothalamus to the adenohypophysis.

The release of ACTH depends in part upon blood corticoid levels (feedback mechanism of Sayers). Under "stress" the rapid release of ACTH is independent of the concentration of blood corticoids. The supposition that "stress" effects this release of ACTH through hypothalamic activity alone is probably incorrect. Section of the pituitary stalk in the rabbit reduces the lymphopenia which follows restraint or exposure to cold, but the lymphopenia consequent to adrenaline injection or to laparotomy is only slightly depressed. Pituitary transplants also release ACTH under the more severe stresses. Systemic as well as hypothalamic factors appear to govern ACTH release.

Although it releases ACTH, "stress" inhibits the release of thyrotrophin Stalk section abolishes the inhibition of TSH release which occurs after restraint but has no effect on the inhibition of TSH release after laparotomy or thyroxine injection. A duality of control (systemic and hypothalamic) is evident.

The possibility does remain that severe stress may raise the blood concentration of a hypothalamic neurohumor to levels high enough to affect the adenohypophysis by the systemic circulation in the stalk-sectioned animal. If this were the case, the control of ACTH release in "stress" would be almost entirely due to hypothalamic activity.

ALLAN H. MILOFSKY

April 27, 1955

THE GENERATION OF BIOELECTRIC POTENTIALS. By Harry Grundfest, Department of Neurology, Columbia University College of Physicians and Surgeons.

It can be shown by microinjection technique of the squid giant axon and by the investigation of electroplacks of electric eels that the mechanism postulated by Hodgkin and Huxley in describing the generation of spike potentials in electrically stimulated nerves is not sufficient for explaining

the generation of all biological potentials. The resting potential is not a simple physico-chemical system whose effects can be explained by the Donnan Equilibrium, but rather a potential closely linked to the spike generator though not in a simple relationship.

Anodal stimulation of electroplacks does not stimulate the cell. It is possible in an esserinized cell to elicit graded local responses which reach overshoot levels yet do not generate a propagated spike. While the cell is refractory to electrical stimulation, it can still produce a response to a nerve volley. This postsynaptic response is graded and not subject to the refractoriness of the electrical response. Perhaps it is never stimulated by an electrical response. This would suggest two separate mechanisms producing two different types of potentials. There is some pharmacological evidence to support this view. Eccles has suggested that the postsynaptic response is accounted for by a change in the semi-permeability to chloride.

It is proposed that there are several mechanisms and types of generators which are responsible for bioelectric potentials found in nature and that these vary according to the type of cell in question. These at least are: (1) the resting potential; (2) spike response, electrically excitable either graded or explosive (propagated); (3) nerve excited response which is graded and due to depolarization or hyperpolarization, and may be explicable by a selective (e.g. Cl) or nonselective permeability change; and, finally, combinations of these depending upon the system studied.

ZOOLOGICAL JOURNAL CLUB

April 22, 1955

BRAIN SIZE AND ANIMAL INTELLIGENCE. By Bernhard Rensch, University of Muenster, Germany.

In evolution, animals of any related group often tend towards a successive increase in size (Cope's Rule). The brain's absolute size increases, too, though it has often been pointed out that its relative size decreases. However, brain growth is not isometric, and it appears that the more complex and higher brain centers do show positive allometry. Further, increase in absolute brain size provides for a greater number of neurons, more connections, and, one might expect, an enhancement of perceptive and retentive prowesses.

Among insects, our experiments have shown that large species have more complex corpora pendunculata than related and smaller species. This does affect behaviour. The larger wasps and bees generally show a more complex social life, which, at least among European species, the smaller ones may lack. Similarity, with certain beetles, where the larger species may not be matched by smaller genera in the care they show for their eggs and in the complexity of their breeding instincts.

In vertebrates, too, higher brain centers show positive allometry. In ontogeny, the positive growth rates may become negative shortly after birth, but lower centers regularly remain negatively allometric. Different races of the domestic fowl show no differences in the relative size of the

entire brain, though the larger races show an increase in the relative size of the more complex integrative areas. Similarly, with increasing body size, the individual neurons in the central nervous system show an increase in size and in the number of their ramifications. Smaller species have many fewer sensory cells, too. Thus, larger animals have superior resolving power and can react to smaller aspects of a stimulus.

Our experiments with rodents and rabbits suggested that the larger species could learn more complicated tasks and could retain them for longer periods. This may be due to the larger neurons and their greater number of dendrites, providing for more switch mechanisms. This does suggest that memory is related to brain and neuron size, in contrast to some modern concepts.

The development of behaviour is subsequent to morphologic changes in the brain. The Broca speech center, for example, is positively allometric. It does not become "filled" with behaviour, however, until after its development. This may account for the length of time which had to pass before human evolution could proceed apace.

P. K.

YALE MEDICAL SOCIETY

May 23, 1955

Presentation of Theses of Fourth-Year Medical Students

RADIATION AND VIRUS MORPHOLOGY: INTERFERENCE IN INFLUENZA VIRUS. By Wilson F. Powell.

Ionizing radiation can be a very useful tool in the assessment of the internal structure of viruses if care is taken to preserve the spacial distribution of energy loss which occurs in the irradiated system.

Freeze-dried samples of Influenza A (Melbourne strain) were irradiated with fast electrons, deuterons, and alpha particles, and assayed for interference with the growth of infective Influenza virus in the chorio-allantoic membrane of the developing chick embryo. All of the inactivations were semilogarithmic with dose, permitting the results to be analyzed in terms of target theory. The sensitive volume for the unit responsible for interference with the liberation of infective virus has a molecular weight of about 1.6 million and probably is formed from one or more molecules folded into the shape of a shell 250 Å in diameter and 14 Å thick. The energy in three ion pairs must be liberated in this volume to produce an inactivation.

The radiation sensitive volume for interference by "incomplete" virus is the same as that for inactivated "standard" preparations. Radiation parameters were the same whether Mel, NWS, or Lee was used as the challenging agent and whether interference was assayed by measuring the rate of intracellular hemagglutinin or "soluble" complement-fixing antigen production, or the liberated virus.

The ultraviolet action spectrum for interference suggests that this unit is principally a protein with a number of aromatic amino acid groups.

A composite structure of influenza virus from irradiation data on infectivity, hemagglutination, and interference was presented. The agreement with electron-microscope structure is quite good. If used with the proper precautions, ionizing radiation is a most valuable physical technique for the study of the functional structure of macromolecules.

WILSON F. POWELL

ELECTRICAL FIELDS OF FORCED VENTRICULAR EXTRASYSTOLES. By Sherwin B. Nuland.

Einthoven's equilateral triangle, a basic principle of electrocardiography, depends for its validity on the concept of its originator and others that the heart behaves as a two-pole source of current lying in the homogeneously conducting thorax. Such a current source should produce an electrical potential distribution on the chest that is bipolar and symmetrically arranged on either side of a line of zero potential, with one side positive and the other negative, the two halves being connected by a straight line, the electrical axis, which rotates from moment to moment during the cardiac cycle. Several workers have already shown that the potential distribution produced by the heart is in reality quite different from that postulated by Einthoven. To investigate the complicated and almost bizarre nature of the distribution a simple "artificial" electrical field was experimentally created by forcing an extrasystole from the center of each ventricle at a known instant in the cardiac cycle of dogs. The field so produced proved to be very similar to Einthoven's above described formulations except that it exhibited no movement during the cardiac cycle. Certain interpretations are made:

1. Under certain conditions the heart is capable of assuming a bipole function, even though it does not do so under normal circumstances.

2. The tissues conduct homogeneously, as indicated by the accurate conduction of a bipolar distribution from the heart surface to the chest surface.

3. The stationary character of the field indicates that the spread of excitation is not detectable in the electrocardiogram.

4. The magnitude and direction of deflection of the electrocardiographic beam at any point on the body are dependent on the characteristics of the electrical field at that point.

SHERWIN B. NULAND

BOOK REVIEWS

PRINCIPLES OF INTERNAL MEDICINE. 2d ed. Edited by Harrison, T. R., *et al.* New York, Blakiston Company, Inc., 1954. 1,703 pp. $21.00.

A review of such a text as this, which contains 311 major headings encompassing over 1,700 printed pages and contributions by 85 authors, is a major chore and this reader has assumed that his mission was obviously not to read all of it in detail. This review is based on an approach from two orientations—the reviewer has read carefully those sections with whose content he is reasonably well informed, and, in contrast, has read some of the sections dealing with material about which he has little or no information. In this way a sample of the total text has been considered from the standpoint of a peer and a student.

The general format of the book represents an approach to the study of medicine which implies certain very definite principles of education with which this reviewer is in total agreement. These principles include an understanding of the normal and pathological physiology of disease states, and an approach to specific diseases through the medium of general discussions of disorders and the gradual development of a variety of theses to a final exposition of specific disease entities. In this manner the minutiae are properly relegated to a position of lesser prominence and the student is encouraged to consider and understand general principles.

The sections on the posterior pituitary gland and on fluid and electrolyte therapy, as well as the section on the kidneys, are all excellent. The discussion of disordered renal function approaches renal physiology in a less meticulous fashion than might be desired. The concepts of "threshold" and "non-threshold" substances seem to linger; the terms "acids" and "bases" are used in an historically older context and the more appropriate semantic representations of acids and bases are not included. This is true in the section on fluid and electrolyte balance, and in the section dealing with changes in electrolyte composition as well. In the section on disordered renal function the reabsorption of solutes and water is described as a back-diffusion process encouraged by the diminished hydrostatic pressure within the venous system of the peritubular blood vessels and the increased colloid osmotic pressure of the blood traversing these vessels. This implies that the fluid in the tubular lumen and the blood stream are in a direct dynamic equilibrium relationship and implies that the tubular epithelium is playing a rather mendicant rôle as an inert and "dead" membrane. The evidence suggests certainly that this is most unlikely. In the section on fluid and electrolyte balance the reviewer has one major criticism which has to do with the over-interpretation of physical signs. The discrimination between subcutaneous edema and intracellular edema on the basis of the presence or absence of thumb prints seems a little unlikely as a proper guide to alterations in the effective osmotic pressure of the body fluids. The sections that are discussed above are, however, in general informative and the bibliography will lead the reader to more complete expositions of the material and will allow the opportunity for self-education.

The sections read by this reviewer concerning which he feels ill-informed were varied and in almost all instances they provided information in a succinct manner, but left the reader with the impression that the discussion was

far from complete. This, of course, is inevitable in such a text and, in fact, it is highly desirable since it should motivate the reader to seek further information. Appropriate sources for further reading are provided in the carefully selected bibliographies.

In the course of his reading the reviewer had many occasions to use the index and found it to be quite complete and providing a rather untroubled use of the textual material.

In summary, within the limits that must always be imposed on a text which encompasses as much material as is represented by this book, the reviewer finds it a quite satisfactory and worthwhile introduction to the study of medicine and one which should be of value to all of us who are students and practitioners.

L. G. WELT

PEDIATRIC DIAGNOSIS. By Morris Green and Julius P. Richmond. Philadelphia and London, W. B. Saunders and Company, 1954. 436 pp. $10.00.

Doctors Green and Richmond, both professors of pediatrics familiar with the dual requirements of clinical service and educational responsibilities, have prepared this new book on pediatric diagnosis dedicated to "those who care for children everywhere." Their objective is to help "students and practitioners to increase their diagnostic skill through a systematic and integrated approach to patient study that can be readily applied at the bedside or in the office." The emphasis is on "competence in history taking and physical examination; on the accomplishment of *early* diagnosis; on the application of information from the basic sciences to clinical situations; on the development of a functional knowledge of physical, physiologic and psychologic growth and development; and on differential diagnosis."

In an initial brief but perceptive essay on pediatric history, helpful observations and suggestions are expressed regarding techniques of interviewing. The authors stress the importance of putting parents and patients at ease, the opportunities to learn by attentively listening and observing during the interview, and the physician's rôle as a promoter of health rather than exclusively as a healer of the sick.

The main body of the book is devoted to extensive sections on the physical examination and on signs and symptoms. In the first of these, an introductory essay on special features of the pediatric physical examination is followed by a series of detailed evaluations organized on the basis of familiar anatomical categories. In the section on the neurological examination, however, special consideration is given to neurological injury in the newborn infant, cerebral palsy, meningitis and meningismus, as well as to evaluation of the cranial nerves and spinal cord. A chapter on developmental neurology written by Dr. Sally Provence of the Child Study Center at Yale is another special feature which provides a concise and informative indication of what can be accomplished without elaborate training or techniques in assessing and interpreting the behaviour and performance of infants and young children.

Throughout the section of the book organized to approach diagnosis from the standpoint of signs and symptoms, recognition is given to the significance

of growth and development as the chief features which distinguish infants and children from adults. This section includes somewhat diverse subdivisions on disturbances of growth, constitutional signs and symptoms such as fever and edema, symptoms referable to particular systems such as the urinary tract, and symptoms related to sexual development and to intellectual retardation. Within each subdivision of this section an attempt is made to list the conditions in which the designated symptom is encountered and to present some information concerning the mechanism of its development. These explanations are necessarily brief and were not intended to be complete; they vary considerably in effectiveness.

The final section on health supervision gives consideration to the prenatal period, infancy, the preschool period, the school years, and adolescence. An appendix includes in tabular form familiar percentiles for weight, height, and other selected measurements in different age groups.

The book is attractively composed and in regard to both style and typography is easy to read. Incorporated into the text are numerous up-to-date references which directly accompany the subjects to which they refer. This arrangement, devised by the authors to encourage more intensive study, is an effective innovation. The index, although extensive, could be more serviceable if more complete. For example, the common terms croup, salicylates, hysteria, intoxication, and poisoning are not listed alphabetically; similarly, calcification in the skin is listed but not pulmonary or intracranial calcification.

This book does not pretend to impart new knowledge of pediatrics but rather a new approach to existing knowledge. It will not replace nor was it intended to be a substitute for more comprehensive texts including Gross's *Surgery of infancy and childhood* to which frequent reference is made. Its chief value would seem to be as a guide to further reading and to a better understanding of those aspects of pediatrics with which this book is concerned.

EDWARD C. CURNEN

Shearer's MANUAL OF HUMAN DISSECTION. Charles E. Tobin, Ed. 3d ed. New York, McGraw Hill Book Co., Inc., 1955. xi, 287 pp. $6.00.

The student of anatomy will profit greatly from the use of this revised and refined dissecting room guide provided that he heeds the advice of the editor who warns that "the dissector should use this book in view of the purpose for which it was written—a manual of human dissection. Therefore, the information gained from the dissection and that obtained from the brief descriptions should be supplemented by collateral reading in one of the more standard descriptive texts, if he is to obtain a more thorough understanding of human anatomy."

This counsel is wisely given, for the book contains only the dissection guide text and the anatomical description, in the "regional anatomy" fashion, of the usual major subdivisions of the human body. No attempt is made to elucidate the many structure-function relationships that the student is expected to know, nor is there any mention of various classical, clinical tidbits

of knowledge, such as Colles' fracture, which every medical student is eventually called upon to recite.

The dissecting guide is illustrated with 79 plates, which might well be somewhat larger, in black and white. The type is large and clear with major points emphasized in black, heavy type, thus facilitating review and minimizing the need for underlining. The book is bound so that it lies flat which means that hands soaked in cadaver fixative will not have to reopen the book constantly to the desired page.

A particular merit of the book is the author's success in clearly presenting the highlights of anatomy while omitting, without serious consequence, the bothersome minutiae of detail and lengthy directions for tedious dissection that tend to confound and confuse the beginner. The reviewer speaks here on the basis of his own recent experience in freshman anatomy.

In a large class, with laboratory instructors at a premium, this book will be a particularly useful guide to steer the student through the various fossae and fenestrae of anatomy.

M. M. LOTZ

HISTORICAL REVIEW OF BRITISH OBSTETRICS AND GYNAECOLOGY. By J. M. Munro Kerr, R. W. Johnstone, and Miles H. Phillips. Edinburgh and London, E. & S. Livingstone, Ltd., 1954. 420 pp. $6.75.

Progress in medical science is such that, at a given stage of knowledge, the next logical advance presents itself to a number of different minds. For the historian or for the contemporary writer it is often difficult to assign the credit where it is due.

This task has been undertaken by Senior Fellows of the Royal College of Obstetrics and Gynaecology in a semi-jubilee volume written as a sequel to H. R. Spencer's *History of British Midwifery 1650-1800*. The work is done in a thorough and painstaking fashion with carefully documented accounts of the progress and contributions made by British obstetricians. For a book about the British and by the British, rather generous mention is made of advances from the European continent and America.

Seven-eighths of the book is devoted to obstetrics. The 150 years are divided into three periods, each period being subdivided into chapters on various aspects of midwifery. This is followed by a fourth series of chapters recording the advances in special subjects. In places, this form of organization leads to a disconnected and occasionally repetitious account. Gynecology is limited to four chapters at the end. There is little or no discussion of developments in knowledge of reproduction, sterility, gynecological pathology, genital infections, endocrine abnormalities, or certain aspects of steroid hormones. Ovarian, vulvar, and corpus carcinoma is not mentioned.

As in any volume with multiple contributors, some chapters are more complete than others, but as a whole, it is a dignified account commendably done—as it should be—by men, some of whom have made places for themselves in future histories. There are lengthy discussions as to who should receive the laurels for various obstetrical manoeuvres or who first performed certain operative procedures. Should Credé or Dublin have prior claim to the management of the third stage of labor? Should Donald or

Fothergill be credited with the Manchester pelvic repair? It is pointed out that one may discover and another popularize a new method, or that, as in the case of the "cadaveric particles" of Semmelweis, enlightenment may not be accepted for many years because of unbelievers. History ignores the young assistant or pupil who often is the first to express the idea that later becomes the property of his seniors. The effort to be fair and factually correct is commendable, though at times not very stimulating reading. This is a useful historical reference work rather than an attempt to portray the romance of medicine.

JOHN McLEAN MORRIS

THE PINEAL GLAND. A REVIEW OF THE PHYSIOLOGIC LITERATURE. By Julian I. Kitay and Mark D. Altschule. Published for the Commonwealth Fund. Cambridge, Harvard University Press, 1954. 280 pp. $5.00.

This volume lists over 700 references to the pineal gland and for this alone is an invaluable aid to those who require a ready access to the literature on this organ. The authors have evidently read a majority of these papers and have analyzed them under the various organ systems which at one time or another have been reported to be affected by removal of the pineal gland or injection of extracts made from it. Their study is thorough and the evidence has been carefully reviewed. The conclusion is that while there is some suggestive evidence for the endocrine function of this organ, it is far from satisfactory and their opinion is best expressed in their own words: "Although the available physiologic and clinical data justify the presumption that the gland is functional, its functions cannot yet be defined" (p. 104).

This volume will have made a significant contribution if it encourages others to undertake more extensive and more rigidly controlled studies than have often been the case in the past.

C. N. H. LONG

CONGENITAL SYPHILIS. By David Nabarro. Baltimore, The Williams and Wilkins Company, 1954. 470 pp. $10.00.

This publication seems almost anachronistic since the diagnosis and treatment of congenital syphilis no longer constitutes an important problem. Nonetheless, the decrease in incidence of congenital syphilis has not proceeded to the point of complete eradication, so this problem continues to merit attention.

Nabarro's monograph is based on an experience with over 1,000 cases. A large number of these patients were seen in the pre-penicillin era; thus, this work is in part an historical account of a once prevalent affliction. The subject of congenital syphilis is discussed extensively in terms of pathology, symptomatology, diagnosis, treatment, and prognosis. In general, the discussions are well written and authoritative; they represent a blending of the author's large experience and that reported in the literature. Comprehensive bibliographies are included and would be helpful for further read-

ing. The inclusion of many excellent clinical photographs adds to the book's value.

The book will serve as a good reference and is a valuable addition to the literature on congenital syphilis.

MORRIS GREEN

FAT METABOLISM. V. A. Najjar, Ed. Baltimore, Johns Hopkins Press, 1954. 185 pp. $4.50.

This interesting small volume is divided roughly into two parts; the first deals with clinical and physiological considerations of obesity and hyperlipemia and the second presents current views on the biochemistry of the lipids. The introduction by Najjar is essentially a summary of the topics presented. Gordon discusses psychosomatic aspects of obesity in children and pointed out that regional lipophilia would be difficult to explain on a physiological or biochemical basis. Mayer presents studies on the hypothalamic "glucostatic mechanism" of hunger and inferred from the analogy to gold thioglucose obesity that the standard explanations of obesity produced by overeating may be rather superficial. Hyperlipemia is discussed by Holt and Ahrens with particular reference to an interesting case of idiopathic familial lipemia. Meng presents a most interesting study on maintenance and increase in body weight of animals and humans treated with intravenous emulsions of neutral fat. Anfinsen suggests that deficiency in degradation of low density lipoproteins resulted in their accumulation in plasma; noting that the "plasma clearing" system might be the portion of the homeostatic mechanism for degradation of the low density lipoproteins, he pointed out that the failure of synthesis of heparin, a cofactor in the clearing system, might be responsible for some of the clinical hyperlipemias.

In the section on metabolism, Lipmann briefly discusses the rôle of acetoacetyl-Co A in ketosis. Lehninger outlines reactions of fatty acid synthesis and degradation and points out the interesting finding that the beta-hydroxy butyrate in the urine of fasting and diabetic patients is in the l-form, while that of the sequence of fatty acid degradation is in the d-form; the significance of this finding is not as yet apparent. Gurin studied the failure of the liver slices of diabetic animals to synthesize fat. He indicates that addition of phosphorylated glycolytic intermediates to cell-free preparations of diabetic livers enhanced the rate of synthesis of fat. Kornberg noted that the synthetic and catabolic pathways for glucose and the fatty acids are apparently the same, but are distinctly different for phospholipids. The metabolism of cholesterol is discussed from the standpoint of atherosclerosis by Langdon; the very interesting rôle of cholesterol esterase of the pancreas is touched on only very briefly.

This volume attempts an approach to clinical problems of obesity, hyperlipemia, diabetes, and atherosclerosis via physiology and biochemistry. Although the biochemical aspects have been presented extensively in other symposia, this early and rather incomplete attempt to fuse recent biochemical advances with clinical problems seems very worthwhile.

HARRIS BUSCH

ADMINISTRATIVE MEDICINE. Transactions of the second conference held December 8-10, 1953. George S. Stevenson, Ed. New York, Josiah Macy Jr. Foundation, 1954. 164 pp. $3.00.

Administrative medicine presents an edited summary of a three-day conference of selected leaders in medicine, nursing, education, public health, and sociology. Although the theme of the conference was Administrative Medicine, the discussions actually constituted a potpourri of a wide variety of subjects related to the socio-economic problems involved with general health care in the community.

Discussion jumps from preventive medicine and medical and nursing education and financing to labor health centers, group practice, and medical care plans. Mixed in are observations on human relations in hospitals, general practitioners, and family doctors, and efforts to justify the existence of chiropractors.

This book is not of too much value as a reference text. It is not organized in a way to be particularly helpful although an index has been added. However, it presents the very frank views and opinions of a number of thoughtful students of medical care problems in an informal fashion. If one cannot participate in such a conference, this is the next best method of understanding the views of leaders in this field.

A. W. SNOKE

THE MICROPHYSICAL WORLD. By William Wilson. New York, Philosophical Library, 1954. 216 pp. $3.75.

It is a pleasure to welcome Professor Wilson's little book to the select circle of competent works which interpret modern physical science for the intelligent layman. The theme of the book is clearly expressed in the foreword: "It starts out from a time when atoms and molecules were no more than hypothetical suggestions to account for prominent features of known chemical and physical phenomena, e.g., for the law of constant proportion in the composition of chemical compounds, and it indicates how with the growing knowledge of such phenomena these things gradually became more definite and probable until at last they were found to be indeed real and not hypothetical at all." The level of the approach is intermediate between the popular writings of Jeans and Eddington and those works, such as Born's *Atomic physics,* which are intended for those with professional training in the physical sciences.

Perhaps at times the author is a bit too dogmatic about hypotheses which at the moment rest on rather unsubstantial grounds. The mass of the universe, for example, is certainly a much more speculative subject than his treatment of it would indicate. However, this objection can be raised in only a very few instances; and indeed, he points out how frequently rash speculation at one time becomes established fact.

An unusual feature of the book is the liberal use of names and thumbnail remarks about the scientists whose work is under discussion. It is worthwhile to hear that the J. J. Balmer who discovered the relations between the lines of the hydrogen spectrum was a Swiss schoolmaster, and that

C. T. R. Wilson first began his investigations into clouds, which culminated with the discovery of the cloud chamber, because of his interest in the optical phenomena seen in the mists surrounding Ben Vevis in Scotland. Such touches bring home the fact that physics has as warm and as human a history as any of man's endeavors and not the cold barrenness envisioned by many.

The book can be recommended to a biologist or medical man who wishes to gain insight into atomic and molecular physics. The format of the book is pleasing and it is well printed, but the price is excessive in view of those asked by other publishers.

F. HUTCHINSON

TREPONEMATOSES: A WORLD PROBLEM. By T. Guthe and R. R. Willcox. Geneva, World Health Organization, 1954. 79 pp. $.50.

This brochure is an extended and well-illustrated memorandum dealing very unequally with two problems. It is a succinct and interesting exposition of the view that control of the human spirochetal diseases is best achieved if they be regarded as a unit. Since today they are all primarily contact diseases effectively treated, aborted, and prevented by penicillin, this concept has the advantage of simplicity and of answering the main needs of those whose primary interest lies in control. Some detailed data are given on the nature of successful campaigns, the lessons learned from failures to follow through after initial surveys and treatment campaigns, and the necessity for a permanent even though reduced force to continue treatment on the contagious residue.

The pamphlet also exposes, and very inadequately, a view which this reviewer thinks is untenable even when presented brilliantly. In essence this concept holds that since the spirochetes have not been distinguished by sufficient criteria, the diseases are the same—i.e., essentially a unitarian view. In general, adherents of this view emphasize less the identity of syphilis, yaws, and pinta—wrongly, it seems from their point of view—than they do the identity of syphilis and various contact spirochetoses, with age predominance in children, and known locally as bejel (Iraq), dichuchwa (Bechuanaland), njovera (Southern Rhodesia), and the "non-venereal syphilis of Bosnia." Now these clinical entities are not typical syphilis: there is no chancre, no congenital manifestations, and conclusions as to late cardiovascular and neurological involvement are not uniform. Nonetheless the authors group them into an entity which they call "endemic syphilis." The syphilis which we have known for over four centuries is now to be called sporadic syphilis for reasons not explained by the authors and inexplicable to the reviewer.

This rather bizarre redefinition of medical nomenclature would substitute imprecise concepts for those of some degree of clarity, contradictory terms for those which are at least selfconsistent, and deny the evidence of clinical and pathological observation.

The justification for this most peculiar proposal appears to be the notion that if syphilis is non-venereally transmitted, then it will be, or may be,

different in manifestation and in outcome than if contacted during intercourse. Since in either case the portal of entry is mucosal or cutaneous, this view holds that passage through the tissue of the genitalia will exert on *T. pallidum* a profound effect which passage through the tissue of the cheek or mouth will not do. Now this is an extremely important microbiological concept for which one would like to see some evidence presented. Furthermore, in the absence of treatment, precisely how this childhood syphilis is supposed not to be transmitted venereally when the child becomes an adult is never made clear.

To this reviewer the concept, despite its "unity," complicates rather than clarifies the subject, and in addition is confused and unjustified. It is unfortunate that the matter was even raised, for it forms no essential part of this pamphlet.

DAVID WEINMAN

VIRAL AND RICKETTSIAL DISEASES OF THE SKIN, EYE AND MUCOUS MEMBRANES OF MAN. By Harvey Blank and Geoffrey Rake. Boston, Little, Brown, and Co., 1955. 285 pp. $8.50.

We might consider this treatise to be directed to medical student, clinician, and virologist alike as a necessary complement to existing texts that deal with clinical manifestations of viral and rickettsial diseases of man and of animals.

Much can be said to the credit of this book. For one thing, the illustrations are superb. There are 62 figures (mostly halftones) and 7 excellent color plates showing many of the clinical conditions described in the text. The fact that many of the pictures have never been published before makes the book a valuable possession. To mention only a few, there are severe hemorrhagic herpes zoster of the thigh, tissue culture infected with chicken pox virus, moist warts of the genitalia, titration of orf virus (contagious ecthyma of sheep) in the skin of a lamb, and herpes simplex lesions on the palm and on the thigh of adults.

The chapter on warts is especially good, for it is the first time that such a complete account has appeared in a virology text. Other diseases discussed are herpes simplex, the pox group (with a thorough treatment of cowpox), the exanthemata, common cold, herpangina, molluscum contagiosum, epidemic keratoconjunctivitis, and rickettsioses—those contracted by man from animals, and those caused by the Chlamydozoaceae. Some diseases that might have been considered have been omitted. To quote from the preface, "Such exclusions are based on two grounds. In the first category, although the all-inclusive term 'eye' is used in the title, the authors have not thought fit to discuss such diseases as rabies, encephalitis, poliomyelitis, or lymphocytic choriomeningitis which influence the eye for the most part outside the bulb, namely, in the optic nerve, optic pathways, or extra-ocular muscles. The second category includes such diseases as influenza, yellow fever or sandfly fever, in which only conjunctivitis, and that as a somewhat rare complication, would suggest inclusion." The omissions do not, however, detract seriously from the value of the book.

It is unfortunate that the prose is so uneven. Some sentences are clumsily constructed, causing attention to turn from the subject under discussion to matters of English usage and style. Occasionally there is a slightly overgenerous use of commas making the mind and eye stumble and halt at times. Perhaps the revision entailed in a second edition will include some comma culling.

Although most statements are backed by ample bibliography, occasional facts are not, and this prevents the work from being used as a complete reference text. Thus in some instances one will find it necessary to dig his own way through the literature. However, there is no implication in this criticism that the authenticity of the data is in doubt, for both Dr. Blank and Dr. Rake know their subject well.

LISBETH M. KRAFT

A Methodological, Psychiatric and Statistical Study of a Large Swedish Rural Population. By Tage Larson and Torsten Sjogren. Copenhagen, Ejnar Munksgaard, 1954. *Acta Psychiatrica et Neurologica Scandinavica,* Supplementum 89, 250 pp. $3.75.

Sweden has a long history of keeping careful population statistics including the compulsory parish registry of cases of mental disease and mental deficiency. This text covers 45 years of registration (1900-1944) of a Swedish rural area with about 25,000 inhabitants and includes 1,312 registered cases of psychosis, severe psychopathy, severe mental deficiency, and suicide. Data come not only from the parish registries but from institutions dealing with these patients and include not only individuals residing in the area, but those born in the area who have moved away, as well as relatives, ancestors and related members of consanguineous marriages comprising nearly 20,000 registered individuals. The incidence figures resemble those obtained in most comparable investigations except for a higher age at onset for catatonic (35 years) and paranoid (46 years) schizophrenia, and manic-depressive psychosis (40.4 years for women and 42.4 years for men). Unfortunately, there is no way of checking the diagnostic labeling or the number of years that the condition might have been present before coming to medical or statistical attention. One finding that bears further investigation is the additional diagnosis of mental deficiency in 10 per cent of the schizophrenic patients.

This volume will probably be of greater interest to demographers than to psychiatrists, since it emphasizes problems of a purely methodological nature that are always connected with population-studies and family investigations. Nonetheless, the field of psychiatry still suffers from an inadequate statistical baseline and this is a conscientious attempt in this direction. Its interest is limited by a failure to discuss results from any viewpoint except the genetic and by a failure to delineate psychiatric criteria as adequately as statistical criteria.

EUGENE B. BRODY

THE STATUS OF MULTIPLE SCLEROSIS. Roy Waldo Minor, Ed. *Annals of the New York Academy of Sciences,* Vol. 58, Pages 541-720. New York, Academy of Sciences, 1954. $4.50.

This volume is a collection of papers presented at a conference on the status of multiple sclerosis held by the Section of Biology of the New York Academy of Sciences and the National Multiple Sclerosis Society, April 17 and 18, 1953. There are twenty-one papers by thirty-six authors divided into three sections, biological and pathological, biochemical, and clinical methods. No attempt was made to cover the entire subject of this disease with regard to pathology, clinical manifestations, diagnosis and treatment, the papers being mainly presentations of recent advances and work in progress. The quality throughout is quite variable. This collection might be regarded as supplementary to the volume on *Multiple Sclerosis and the Demyelinating Diseases* published in 1950 by the Association for Research in Nervous and Mental Disease based on the 1948 conference.

The first two sections on biological and biochemical methods emphasize the recent experimental approach to the pathogenesis and manifestations of the disease. Significant reports are those on genetically controlled demyelination and the problem of regeneration in the spinal cord. There has been much experimental work recently concerning the rôle of allergy in relation to demyelinating disease. Although there are many resemblances between experimental allergic encephalomyelitis and multiple sclerosis, there are enough differences to indicate that the disease processes are not actually the same. In this present volume it is reported that patients with multiple sclerosis and acute disseminated encephalomyelitis do not have skin sensitivity to allergens prepared from human nervous tissue. Certain metabolic findings in patients with multiple sclerosis were reported which indicate the possibility of derangements in intermediary carbohydrate and protein metabolism. An abnormal response to oral glucose with elevation of pyruvic acid and a low serum acid ATPase activity were found. High serum cholinesterase values were observed in men having a progressive disease, and lower values than normal appeared with a remissive condition. The distribution of amino acids in the cerebrospinal fluid was determined by paper chromatography, and it now remains to determine whether there are any abnormalities in this distribution related to diseases of the nervous system. Characteristic changes in the protein fractions in the blood serum and cerebrospinal fluid in patients with multiple sclerosis have been demonstrated. Further studies concerning the increased gamma globulin content of the cerebrospinal fluid in this disorder were presented. This is a more sensitive determination than the colloidal gold curve and it has been shown that a significant increase in gamma globulin occurs in almost 70% of patients with this disease. This finding is not pathognomonic since it occurs in neurosyphilis and rarely in other non-specific neurological disorders, aside from illnesses such as multiple myeloma. Low serum albumin and albumin-globulin ratios also occur. It is hoped that these biochemical changes will be further verified and prove of significant diagnostic value aside from hints that they may give concerning the pathogenesis of this disorder.

The problems of evaluating therapy in a disease with spontaneous fluctuations in course are extremely difficult. This monograph contains a review of recent pharmacological agents utilized in the treatment of multiple sclerosis. It is concluded that there are as yet no specific therapeutic agents which cure the disease, but that much benefit can be obtained through symptomatic treatment in individual cases. A study of the short- and long-term effects of adrenal steroids on the clinical patterns of multiple sclerosis was presented, and although certain changes in motor symptoms occurred, it was felt that the hormones were not suitable therapeutic agents. An attempt at using muscle adenylic acid was inconclusive.

Studies of environmental factors again emphasized that the incidence of the disease was much higher and the onset earlier in northern climates. The average life expectancy is now regarded to be at least 21 years after onset. Also, it is now concluded that this illness, once started, runs its course regardless of any obvious social or environmental factors.

The way towards further research is helped by reports such as this; however, the volume is merely a compilation of selected papers and is not a complete critical review. It therefore has essentially a limited value but it does represent a milestone in the pathway of progress of knowledge concerning this common disorder of the nervous system.

GILBERT H. GLASER

an ESTABLISHED dosage form
of choice
for PROVED broad-spectrum
antibiotic therapy

TERRAMYCIN®

Brand of oxytetracycline

INTRAMUSCULAR

the *first* broad-spectrum antibiotic
available in this convenient parenteral form
for the treatment of a wide range
of infections due to susceptible organisms.

Supplied in single-dose vials. On reconstitution,
each single dose contains: Crystalline
Terramycin hydrochloride—100 mg.
Magnesium chloride—5%
Procaine hydrochloride—2%

Pfizer

PFIZER LABORATORIES, *Brooklyn 6, N. Y.*
Division, Chas. Pfizer & Co., Inc.

NEW 2ND (MAY 1955) EDITION

MICROBIOLOGY

By FLORENE C. KELLY, M.S., Ph.D.

Professor of Bacteriology, University of Oklahoma School of Medicine;
Formerly Assistant Professor, Dept. of Biology, Simmons College, Boston

and K. EILEEN HITE, Ph.D., M.D.

Formerly Assistant Professor Bacteriology, The University of Chicago

With Introduction by G. M. DACK, Ph.D., M.D.

Professor of Bacteriology, The University of Chicago

In this new 2nd edition, the authors have carefully revised the entire text to incorporate a great deal of new material and delete that which has become outdated.

The carefully planned organization introduces the student to a general coverage of the microscopic world before proceeding to the detailed study of the large phylogenetic groups of microorganisms, their biology and interrelationships, bacterial physiology, microbial populations and their control, as well as methods for their study. In approximately the last half of the book, the authors discuss parasitism and disease, immunity and the pathogenic bacteria, viruses, rickettsiae, fungi and protozoa. In this section they cover the bacteriology of milk, food, water, and air in their proper perspective in an introductory text of this type.

A helpful appendix covers the important technical methods of bacteriology and will serve as an adjunct to the laboratory study of bacteria and microscopic fungi. It concludes with a brief listing of the historical milestones in microbiology.

Bibliographic references to summarizing articles and to comprehensive texts are now more logically placed at the end of each chapter.

Many fine illustrations are particularly helpful.

2nd Edition - May 1955 - 615 Pages - 207 Figures and Tables - $7.50

OTHER PRACTICAL TITLES

Raffel's **IMMUNITY, HYPERSENSITIVITY, and SEROLOGY**
1st Edition. April 1953. 531 Pages. 48 Illustrations. $8.00

Smith & Conant's **ZINSSER TEXTBOOK OF BACTERIOLOGY**
10th Edition. Aug. 1952. 1028 Pages. 425 Illustrations and Tables. $11.00

Belding's **TEXTBOOK OF CLINICAL PARASITOLOGY**
2nd Edition. Publ. March 1952. 1148 Pages. 1015 Illus. and Tables. $12.00

Kolmer's **APPROVED LABORATORY TECHNIC**
5th Edition. 1193 Pages. 481 Illustrations and Tables. $12.00

Gonzales **LEGAL MEDICINE, PATHOLOGY and TOXICOLOGY**
2nd Edition. 1370 Pages. 658 Illustrations. $22.00

ORDER THROUGH BOOK STORES, BOOK SELLERS OR THE PUBLISHER

APPLETON-CENTURY-CROFTS, Inc.

35 WEST 32nd STREET, NEW YORK 1, N. Y.

(Publishers of THE NEW CENTURY CYCLOPEDIA OF NAMES)